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TRANSACTIONS OF THE

SECTION ON

Practice of Medicine

of the
American Medical Association
at the Sixty-Fifth Annual
Session, held at Atlantic City,
N. J., June 23 to 26, 1914

AMERICAN MEDICAL ASSOCIATION PRESS
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LIST OF OFFICERS

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PROCEEDINGS OF THE SECTION

Tuesday, June 23—Afternoon

The meeting was called to order by the chairman, Dr. Charles Lyman Greene, St. Paul, Minn.

Dr. H. B. Hiatt, High Point, N. C., and Dr. William Allan, Charlotte, N. C., presented a paper entitled "Will Sprue Become Endemic in the United States? Notes on Cases Invalided from the Tropics." Discussed by Drs. Roger S. Morris, Clifton Springs, N. Y., and H. B. Hiatt, High Point, N. C.

Dr. Tom A. Williams, Washington, D. C., read a paper on "The Syndrome of Adrenal Insufficiency." Discussed by Drs. Frank R. Starkey, Philadelphia; Walter L. Bierring, Des Moines, Iowa, and Tom A. Williams, Washington, D. C.

Dr. George Douglas Head, Minneapolis, read a paper on "Neurasthenia and Tuberculosis (Concealed)." Discussed by Drs. Nathan Rosewater, Cleveland; F. M. Pottenger, Monrovia, Cal.; Charles Stover, Amsterdam, N. Y.; Eliza M. Mosher, Brooklyn, N. Y.; A. J. Caffrey, Milwaukee; John Ritter, Chicago; Tom A. Williams, Washington, D. C.; Walter B. Swift, Boston; Albert Robin, Wilmington, Del.; H. S. Plummer, Rochester, Minn.; J. P. Munroe, Charlotte, N. C.; Robert N. Willson, Philadelphia, and George Douglas Head, Minneapolis.

Dr. Arthur F. Chace and Dr. M. S. Fine, New York, presented a paper on "The Use of Atophan and Radium Emanation in the Treatment of Gout and the Arthritides." Discussed by Drs. Charles G. Stockton, Buffalo, N. Y.; S. Solis Cohen, Philadelphia, and Arthur F. Chace, New York.

Dr. Louis G. Heyn, Cincinnati, O., read a paper on "Satisfactory Results from Intrarectal Administration of Sodium Salicylate in Acute Rheumatic Fever." Discussed by Drs. E. W. Mitchell, Cincinnati, O.; Joseph L. Miller, Chicago; J. N. Upshur, Richmond, Va.; J. M. Rector, Columbus, O.; James C. Tyson, Philadelphia; Nathan Rosewater, Cleveland, O.; W. W. Tompkins, Charleston, W. Va. and Louis G. Heyn, Cincinnati, O.

Wednesday, June 24—Morning

The Chairman appointed a nominating committee to report at a subsequent meeting, consisting of Drs. Joseph L. Miller, Chicago; W. S. Thayer, Baltimore, and Alexander Lambert, New York.

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A joint meeting was held with the Sections on Pathology and Physiology and Pharmacology and Therapeutics.

The following papers were read as a Symposium on Nutrition:

Prof. L. B. Mendel, New Haven, Conn.: "The Specificity of the Nutrients."

Prof. Otto Folin, Boston: "The Intermediary Metabolism."

Prof. Graham Lusk, New York: "The Specific Dynamic Action of Food."

Dr. Eugene F. Du Bois, New York: "The Total Energy Requirements in Disease as Determined by Calorimetric Observations."

These four papers were discussed by Drs. Victor C. Vaughan, Ann Arbor, Mich.; S. J. Meltzer, New York; F. M. Pottenger, Monrovia, Cal.; E. P. Joslin, Boston; A. D. Eustis, New Orleans; George Douglas Head, Minneapolis; A. J. Carlson, Chicago; L. B. Mendel, New Haven, Conn.; Otto Folin, Boston; Graham Lusk, New York, and Eugene F. Du Bois, New York.

Wednesday, June 24—Afternoon

Dr. Robert N. Willson, Philadelphia, read a paper on "The Heart in the Pneumonias." Discussed by Drs. James M. Anders, Philadelphia; W. S. Thayer, Baltimore, and Robert N. Willson, Philadelphia.

Drs. C. Frothingham, Jr. and W. G. Smillie, Boston, presented a paper on "Effect of Low and High Nitrogen Diet on Renal Function Tests in Chronic Nephritis." Discussed by Drs. L. G. Rowntree, Baltimore; De Lancey Rochester, Buffalo; L. F. Bishop, New York; L. Jonas, Philadelphia; Walter L. Bierring, Des Moines, Iowa, and C. Frothingham, Jr., Boston.

Drs. Harlow Brooks and John Carrol, New York, presented a paper on "The Treatment of Heart Involvement in Syphilis."

Dr. Richard C. Cabot, Boston, read a paper on "The Four Common Types of Heart Disease."

Dr. Alfred Stengel, Philadelphia, read a paper on "Cardiovascular and Renal Responsibility in the Disturbances of Cardiorenal Disease."

These three papers were discussed by Drs. Emanuel Libman, New York; S. Solis Cohen, Philadelphia; Charles Williamson, Chicago; H. S. Plummer, Rochester, Minn.; L. F. Bishop, New York; Robert N. Willson, Philadelphia; Graham E. Henson, Jacksonville, Fla.; Richard C. Cabot, Boston; Harlow Brooks, New York, and Alfred Stengel, Philadelphia.

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Drs. L. G. Rowntree, Allen Chesney and E. K. Marshall, Jr., Baltimore, presented a paper on "Studies in Liver Function." Discussed by Dr. William S. Thayer, Baltimore.

THURSDAY, JUNE 25—MORNING

The following officers were elected: Chairman, Dr. Thomas McCrae, Philadelphia; Vice-Chairman, Dr. John L. Dawson; Charleston, S. C.; Secretary, Dr. Roger S. Morris, Clifton Springs, N. Y.; Delegate, Dr. Richard C. Cabot, Boston, and Alternate, Dr. E. E. Irons, Chicago.

Dr. Elliott P. Joslin, Boston, read a paper on "End Results in Gastric and Duodenal Ulcer."

Dr. Frank Smithies, Chicago, read a paper on "Gastric Cancer in the Young: A Study of Fourteen Cases in Patients Under the Age of Thirty-One."

These two papers were discussed by Drs. J. N. Hall, Denver; F. B. Lund, Boston; Frank Billings, Chicago; J. A. Lichty, Pittsburgh; Alexander Lambert, New York; F. A. Speik, Los Angeles; Allen A. Jones, Buffalo, N. Y.; J. R. Verbrycke, Washington, D. C.; Anthony Bassler, New York; George Douglas Head, Minneapolis; M. H. Fussell, Philadelphia; J. M. Rector, Columbus, O.; J. D. Dunham, Columbus, O.; Elliott P. Joslin, Boston, and Frank Smithies, Chicago.

Dr. Frank Billings, Chicago, read a paper on "Focal Infection: Its Broader Application in the Etiology of General Disease."

Dr. E. C. Rosenow, Chicago, read a paper on "The Newer Bacteriology of Various Infections Determined by Special Methods."

These two papers were discussed by Drs. William S. Thayer, Baltimore; A. C. Griffith, Kansas City, Mo.; Frank Smithies, Chicago; Emanuel Libman, New York; James M. Anders, Philadelphia; De Lancey Rochester, Buffalo, N. Y.; Alfred Stengel, Philadelphia; Harvey D. Wood, Fayetteville, Ark.; J. B. Guthrie, New Orleans; Frank Billings, Chicago, and E. C. Rosenow, Chicago.

Dr. C. F. Hoover, Cleveland, O., read a paper on "The Dead Space and Alveolar Air in Emphysema and Bronchial Asthma." Discussed by Drs. Allen A. Jones, Buffalo, N. Y.; George N. Jack, Buffalo, N. Y., and C. F. Hoover, Cleveland, Ohio.

THURSDAY, JUNE 25—AFTERNOON

Dr. Henry F. Stoll, Hartford, Conn., read a paper on "Late Manifestations of Inherited Syphilis with Especial Reference to Arterial Disease." Discussed by Drs. Robert N. Willson, Philadelphia; W. Y. Watson, Baltimore; A. C. Griffith, Kansas City, Mo., and Henry F. Stoll, Hartford, Conn.

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Dr. W. E. Robertson and Dr. J. V. Klauder, Philadelphia, presented a paper on "Various Types of Lues: A Clinical and Laboratory Study; the Abelin Reaction; Direct Subdural Injections." Discussed by Drs. E. L. Tuohy, Duluth, Minn.; B. F. Diseroad, Philadelphia; A. J. Caffrey, Milwaukee, Wis.; J. V. Klauder, Philadelphia; W. W. Tompkins, Charleston, W. Va., and W. E. Robertson, Philadelphia.

Dr. Graham E. Henson, Jacksonville, Fla., read a paper entitled "A Study of the Arneth Formula."

Dr. James S. Brotherhood, Clifton Springs, N. Y., read a paper on "Salvarsan in Pernicious Anemia." Discussed by Drs. W. E. Robertson, Philadelphia; W. W. Tompkins, Charleston, W. Va.; Robert N. Willson, Philadelphia; E. Lindeman, New York; T. G. Simonton, Pittsburgh, Pa.; Tom A. Williams, Washington D. C., and James S. Brotherhood, Clifton Springs, N. Y.

Dr. E. Lindeman, New York, read a paper on "The Medical Apparatus of Blood Transfusion by the Syringe-Cannula System Without Skin Incision." Discussed by Drs. G. M. Dorrance, Philadelphia; E. Adolphus Knopf, New York; E. A. Jaffin, Jersey City, N. J., and E. Lindeman, New York.

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NOTES ON CASES OF SPRUE INVALIDED FROM THE TROPICS; WILL IT BECOME ENDEMIC HERE?

H. B. HIATT, M.D.
HIGH POINT, N. C.
AND
W. ALLAN, M.D.
CHARLOTTE, N. C.

It has been shown by Price[1] that of the missionaries sent into tropical countries, a large percentage have to be invalided home; from India 46 per cent., from China 51.5 per cent., from Africa 79 per cent. The rate invalided home for sprue is available only from Central and Southern China, being 2.5 per cent. of those sent home from the former region and 4.5 per cent. from the latter. Harford,[2] a former physician to the Church Missionary Society (England), states that he regards bowel disorders as the most important cause of invaliding, and specifically mentions sprue as a common and serious cause.

To come nearer home, sprue is widely prevalent in Porto Rico,[3] which is being invaded at present by Americans in large numbers.[4] As people suffering with sprue are constantly returning to this country from the tropics, the profession will have to consider this disease both from a clinical and a public health point of view. Inasmuch as many eminent students[5] of tropical medicine consider sprue communicable and even infectious, it may very possibly become

1. Price, G. B.: Brit. Med. Jour., Nov. 15, 1913, p. 1293.
2. Harford, C. F.: Brit. Med. Jour., Nov. 15, 1913, p. 1297.
3. Ashford, B. K.: Am. Jour. Trop. Dis., 1913, i, 146.
4. Census figures give 2303 in year 1910.
5. Manson, Bahr, Begg, etc.

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endemic in the Southern states. The comparatively recent introduction of pellagra into this country and its subsequent very rapid spread in the South, should be a warning to us to study our neighbors' diseases as well as our own.

The present observations are based on three cases of sprue from Porto Rico, two from China and one native case which was in all probability sprue; but, since the latter case passed from observation, it could not be studied at length. The clinical picture of sprue consists chiefly of gastro-intestinal symptoms — stomatitis, flatulence with great distention, diarrhea with large, pale, frothy, acid stools, atrophy of the intestinal mucous membrane with diminution in size of the liver and secondary anemia with loss of weight and strength; the course of the disease is chronic with a marked tendency to relapse.

The sprue stomatitis consists in a red, bald appearance of the tip and edges of the tongue, sometimes nearly all of it being involved. Aphthous ulcers are common. The edges and tip of the tongue become sensitive and the patient often complains of a burning, prickling sensation, even while the tongue is still apparently normal.

The diarrhea starts gradually; is of the early morning type until the case has progressed so far that bowel movements continue throughout the day. Straining and tenesmus are not common, but generally there is moderate pain and discomfort before stool and at other times from the passage of large amounts of gas along the bowel. The large gas production, combined with the atrophy of the intestinal wall and the thinning and weakening of the abdominal muscles, allow great distention, which is uniform over the whole abdomen and which remains constantly present.

The stools are the most characteristic part of the picture. Their bulk is great. The odor is very disagreeable. They may be watery or of the consistency

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of molasses, are putty-colored and have a strongly acid reaction. The fecal matter is intimately impregnated with fine bubbles of gas causing the stool to resemble ordinary apple-float very much in appearance, except for the color. Microscopically, the lack of fat digestion is striking; the numerous fat droplets may show a ring of varying thickness of fatty acid needles around the periphery, indicating that a slight amount of fat cleavage has taken place, but there seems to have been very little saponification. After the ingestion of meat, many meat fibers appear in the feces. Schmidt's hydrobilirubin test was very weakly positive in our cases.

The loss of flesh and strength may determine death from exhaustion. The blood shows a secondary anemia.

REPORTS OF CASES

Case 1 (W. A. 616).—A white man, American, aged 25, single, teacher, was referred by Dr. W. A. Glines of San Juan, Porto Rico, in September, 1911. He had been in the island five years. Family and past history were unimportant. The present trouble started in 1909, as sore mouth and diarrhea, following grip and tonsillitis. His weight dropped from 145 pounds to 100 pounds, and he became so weak and emaciated that he returned to New York state in August, 1910. By March, 1911, he had improved somewhat, had gained 14 pounds and returned to Porto Rico.

Present condition shows weight 95 pounds, temperature 97, systolic blood-pressure 94 mm. Hg. Patient very weak, thin, anemic, with edema of the ankles and with harsh, dry skin. Physical examination negative. Blood shows severe secondary anemia; normal differential count; no plasmodia; urine normal; feces liquid, acid, frothy, composed largely of fats and fatty acids.

He had at various times been on buttermilk, meat, whole milk, no starch diets, etc., and for the past several months has been living on artificially soured whole milk. He complains of numbness of any part of the body on which he lies, from the scalp down, and of cramps of the extremities, and says he cannot think about anything except something to eat. Tongue is sensitive with a raw tip; abdominal distention great. One stool is passed at 2 a. m. always, from three to four before midday, and from two to three between midday and midnight. He sleeps from 9 p. m. to 2 a. m. but rarely after the 2 a. m. stool.

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The patient was put to bed on a milk and grape diet. Sodium bicarbonate enemas were tried but found too exhausting. Several attempts to feed raw eggs convinced us that proteins were harmful at that time. After two weeks in bed he suddenly collapsed, developing an acidosis with air-hunger and acetonuria, and was thought to be dying. Alkali was given by rectum, and after the acidosis subsided enough milk and lactose lemonade were given to supply 1,000 calories daily. The abdominal distention and discomfort were so extreme that we determined to give monosaccharids instead of disaccharids. The only available monosaccharid at the time was glucose from the candy-maker's shop, so this was fed in lemonade, tea, grape-juice and milk. Later, almost raw liver and pancreas soups were added. The patient was discharged from the hospital in November and by February, 1912, had reached 127 pounds. There has been no return of the trouble since.

Case 2 (W. A. 1071).—A white, American woman, aged 42, married, housewife, came to us from Porto Rico in September, 1913. Family history was unimportant. The patient had lived in Porto Rico since 1909. She had had acute rheumatic fever at age of 12, followed by chorea, and later had quinsy; has had joint pains either with or without fever and swelling, severe enough to put her in bed, off and on, for the past thirty years, except when living in the far south, Key West, or San Juan. Present trouble began in February, 1911, with a feeling of fatigue and weakness. Within a month the diarrhea started. The gums and lips became sore in May, 1911, and she lost weight. She took six weeks' milk and rest cure and was well again by July. The second attack started in February, 1912, with laziness, sore tongue and gums and later diarrhea of the early morning type, starting at 2 a. m. and subsiding by noon. She reached twenty stools a day with such abdominal distention that she could not wear some of her clothes. She dragged along in and out of bed until March, 1913, when she became too weak to feed herself and weighed less than 100 pounds. She was out of bed again in June. Since January, 1913, she has taken nothing but milk, except for three weeks in July when she tried a meat diet but without benefit. In March, 1913, she took the yellow santonin treatment until she "saw yellow" and vomited; she was unable to take more than 1 grain every second day; she has taken occasional doses ever since. Present weight is 129 pounds, which is only 15 pounds below her normal weight. Every two hours she is taking a pint of milk up to four quarts a day. Physical examination negative except for the tonsils, which are large and matted down by adhesions from both pillars. Blood shows moderate secondary anemia, normal differential count, no plasmodia. Urine is negative. While

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the case was under observation, worry or fatigue would precipitate diarrhea with the typical acid, frothy, fatty stools; at other times the bowels were normal. At first the patient was put to bed on a milk and monosaccharid diet of grapes, honey and bananas. After a few weeks toast, baked apples and potatoes were added, and later cereals, eggs and cheese. By the middle of November she could be up all day, weighed 135 pounds, was taking solid food three or four times a day instead of milk eight times and her menstrual cycle, which had shortened to three weeks, again became normal. She was advised to visit in the United States until perfectly strong again, but intense homesickness with the difficulty in leading a regular life while visiting from place to place, soon counterbalanced the benefit of a northern latitude, and she returned to Porto Rico in March. The excitement of homecoming precipitated several days' diarrhea again.

Case 3 (H. B. H. 20).—A white woman, aged 32, married, housewife, who had never been out of North Carolina, was seen in July, 1913. Her father had died four years previously of pneumonia superimposed on chronic pellagra. Past history was unimportant. Present trouble started in February, 1913, with a diarrhea which at first consisted of from four to five stools daily, but which, in spite of medication, soon increased to ten or twelve stools daily. The diarrhea started about a month before expected confinement, which occurred several weeks early. An intense burning in the mouth and esophagus was present. She grew steadily worse, and when seen in July, had stomatitis, burning in the esophagus, extreme flatulence, and a diarrhea of from fourteen to twenty stools daily, beginning in the early morning and lasting throughout the day until about 6 p. m., after which she was not troubled until the next morning. The diarrhea was painless and the stools were of a pale yellow, or putty color, very frothy and expelled with a great accompaniment of gas; they had never contained blood. The patient had lost considerable flesh and was much weakened. Examination of chest and extremities was negative. The abdomen was tightly distended with gas, puffed out like a small balloon, and gave a doughy sensation on palpation. The superficial veins were dilated. No skin symptoms have ever been present. The blood showed hemoglobin 65 per cent., red cells 3,200,000; white cells 8,000; smear showed some poikilocytosis, red cells otherwise normal; no plasmodia. Sputum and urine were negative. Feces show a very offensive, voluminous, nearly white acid stool, frothy from the intimate admixture of fine gas bubbles. Microscopic examination showed no ova, no protozoa, many fat droplets and fatty acid crystals, with some splitting of the periphery of the fat droplets.

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The patient was immediately sent to the mountains for the remainder of the hot season. At first, following a careful diet, the improvement was marked. As she improved, however, she became careless in diet and grew worse again. Becoming despondent over this she returned home and placed herself in the hands of my colleague, Dr. Duncan, who advises me that at present she is much improved, having gained greatly in weight and strength. He states that his treatment consisted of a diet of milk and fruits, and that the only medicine to which he could ascribe any beneficial results was iron, given over a long period.

Case 4 (H. B. H. 25).—A white woman, American, aged 38, married, housewife, was referred by Dr. J. T. Burrus of High Point in August, 1913. Family history was negative; past history negative until the patient went to Porto Rico as a missionary in 1904. Within a few months she contracted malaria, which proved so severe she was forced to return to the States. She continued to have one chill a month for a time but finally recovered entirely and returned to Porto Rico in 1906, where she remained until 1909. During these three years she enjoyed good health. The present illness began in May, 1912, three years after she had left the tropics. The first symptoms were slight diarrhea, from three to four stools daily, with some flatulence and stomatitis.

In spite of constant treatment the patient had grown steadily worse during the past eighteen months until, when seen, she weighed only 75 pounds. There was no subcutaneous fat; the dry, harsh skin was drawn tightly over the bony prominences. Mucous membranes were pale, skin muddy, eyeballs prominent from loss of orbital fat, hair lusterless, mouth and tongue the seat of subacute stomatitis. The pharynx and esophagus were not involved; chest and extremities negative; vision and reflexes normal. The abdomen was tensely distended, with thin walls and dilated superficial veins, everywhere tympanitic, and liver dulness obscured; doughy sensation on palpation. Pulse was 80, temperature 98, systolic blood-pressure 94 mm. Hg. Stools from eight to twelve daily, beginning between 12:30 a. m. and 2 a. m., and continuing until noon, with several in the late afternoon. At this time the patient was spending all of her time out of doors on a cot, or walking for short distances; in spite of this full exposure to sunlight there had never been any erythema on the exposed parts. Blood showed hemoglobin 60 per cent., red cells 3,000,000, white cells 4,600, normal differential count, no plasmodia. Urine was normal. Stools large, acid, frothy, putty-colored, no parasites, no occult blood, Schmidt test positive. Microscopically, undigested food, fat droplets, and fatty acid crystals made up the picture.

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The patient was put on a milk and monosaccharid diet, without any medication, and a month later eggs, cereals, baked apples, potatoes, butter, and white meat added. She was permitted to go home under observation in September, and finally discharged in December. At this time she weighed 136 pounds, had a systolic blood-pressure of 119 mm. Hg, felt perfectly well and was having one or two stools a day.

In the treatment of sprue a great number of remedies have been recommended, such as potassium chlorate with morphin and bismuth,[6] powdered cuttlefish bone,[7] colloidal silver,[8] phenyl salicylate (salol), betanaphthol, mercuric chlorid, cyllin, izal (cresol preparations), acetozone and ipecacuanha.[9] A few years ago Begg[10] brought forward yellow santonin as a specific remedy, but Rogers, Manson and Castellani, working in India, have all failed to confirm Begg's results, and Ashford[11] working in Porto Rico, says, "Santonin, therefore, if it has any such specific action as that intimated by Begg, does not seem to be superior to a carefully supervised diet, especially a milk diet."

Rest in bed is obviously essential. The use of any drug as a specific is at present purely empirical. Moderate use of alkali seems rational. In severe cases the exclusive meat diet, or exclusive whole milk diet seems to us irrational. The fruit diet is simply a monosaccharid diet, and this in conjunction with skimmed milk seems to us to be the best diet to use in severe cases. The advent of cold weather, particularly cold nights, has apparently been of greater benefit to our patients than any other single factor. We know that the best treatment for pellagra is removal to the mountains during the hot months, and for the same reasons we think that in active cases of sprue the patients should not attempt to remain in the tide-water or piedmont regions during June, July or August.

6. McDonald, W. C. C.: Australasian Med. Gaz., June, 1911.
7. Cantlie, J.: Brit. Med. Jour., Nov. 15, 1913, p. 1296.
8. Manson, Sir P.: Tropical Diseases, New York, William Wood & Co., 1908, p. 477.
9. Rogers, L.: Dysenteries, Oxford Univ. Press, 1913, p. 320.
10. Begg, C.: Sprue, New York, William Wood & Co., 1912.
11. Ashford, B. K.: Am. Jour. Trop. Dis., 1913, i, 146.

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Stuart,[12] Burnet,[13] Jackson[14] and others,[15] maintain that sprue and pellagra are the same disease, or in other words that sprue is "pellagra sine pellagra." While our experience with sprue is very limited, our experience with pellagra has been considerable, and we see no reason to confuse these two diseases. They have in common sore mouth, diarrhea, secondary anemia, loss of flesh and strength. Sprue has none of the nervous, skin, uterine, vaginal and rectal symptoms of pellagra, while pellagra is not characterized by the distention, and usually not by the early morning type of diarrhea found in sprue. The stools in the two diseases are totally different; the pellagra stool is large and liquid but composed of food remains hurried through the intestinal canal; the intimate admixture of fine bubbles of gas, the intense acidity and the characteristic picture of partially split fats are entirely wanting. We have elsewhere warned against the diagnosis of pellagra on the grounds of sore mouth and diarrhea.[16]

SUMMARY

Cases of sprue are constantly sifting back into this country and should be recognized and treated as such. Sprue should not be confused with pellagra. Rest in bed, a monosaccharid and skimmed milk diet and cold weather seem to be the most important factors in the treatment. Sprue may very possibly be or become endemic in the Southern states.

ABSTRACT OF DISCUSSION

Dr. Roger S. Morris, Clifton Springs, N. Y.: Did Drs. Hiatt and Allen make gastric analyses in their cases or not? The diarrhea which the patients had is described as a morning diarrhea, and it occurs to me that this may have been associated with conditions in the stomach.

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12. Stuart, C. E.: Abstr., Jour. Trop. Med., 1913, xvi, 287.
13. Burnet, J.: Are Pellagra and Sprue One and the Same Disease? Abstr., The Journal A. M. A., Sept. 16, 1911, p. 1014.
14. Jackson, T. W.: Tropical Medicine.
15. Tyson and Fussell: Practice of Medicine, p. 1164.
16. Allan, W.: New York Med. Jour., Dec. 18, 1909.

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Dr. H. B. Hiatt, High Point, N. C.: We made gastric analyses in all cases and nothing in particular was obtained from them. Sometimes we met achlorhydria and sometimes the conditions were normal. The morning diarrhea we considered to be the result of the low blood-pressure. The object of reporting the cases was to call attention to this subject and to utter a warning. If sprue should become endemic in the South its spread might be as rapid and the disease become as common as pellagra.

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NEURASTHENIA AND TUBERCULOSIS (CONCEALED)

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MINNEAPOLIS

Neurasthenia is defined as a condition of exhaustion in the general nervous system. No clear-cut symptom type has ever been described which could identify it and separate it from other diseases, the pathology and etiology of which are known. No specific cause or definite lesion in the brain, spinal cord, peripheral nerves or other organs or tissues of the body have been discovered which would serve to establish a definite pathology for it and thus distinguish it from other diseases the pathology of which is known.

Resting on no etiologic, pathologic or distinctly clinical foundation, the question may pertinently be asked—why does neurasthenia still retain its place as a clinical entity and why do clinicians persist in making the diagnosis of neurasthenia?

Because after the cases of recognizable organic disease simulating neurasthenia have been excluded from the group, a good number remain in which clinicians can detect no tuberculosis, no syphilis, no gastric ulcer, no nephritis, no organic heart-disease, no exophthalmic goiter or other organic disease.

That the limitations of our diagnostic resources may be responsible for this is quite probable because the Wassermann reaction has helped to exclude from the group of so-called neurasthenias many cases of concealed lues; the Roentgen ray has subtracted a number by revealing the presence of unrecognized gastric ulcers, and the more recent methods of cardiac exam-

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ination and diagnosis have taken out a not inconsiderable number of cases of organic heart-disease.

If it can be shown that many of the so-called pure neurasthenias harbor a tuberculous infection so concealed as to have hitherto escaped recognition, the death knell of neurasthenia as a clinical entity must be sounded.

The close relationship between neurasthenia (so-called) and tuberculosis has long been recognized and commented on.

Stiller[1] devotes a whole chapter to the subject.

Lawrason Brown has emphasized the fact that in no disease is the neurasthenic state so frequently encountered as in tuberculosis.

It is not my intention to discuss the relationship between neurasthenia and clinically demonstrable tuberculosis, nor do I intend to consider the cases of clinically recognizable tuberculosis exhibiting neurasthenic symptoms.

The purpose of this study is to present evidence to prove that:

1. Many cases of clinically pure neurasthenia harbor tuberculous lesions so concealed as to escape detection by the examination methods usually employed.

2. No organic disease except tuberculosis can be discovered in these cases.

3. The diagnosis of tuberculosis rather than neurasthenia should be made in these cases.

4. The nervous symptoms exhibited by these patients should be interpreted as a new clinical symptom type for tuberculosis produced by the toxin of the tubercle bacillus.

In proof of this contention I here present the clinical reports of fifteen cases.

The diagnosis of neurasthenia was primarily made in all. The varied subjective symptoms, the long time over which these symptoms had been complained of, the absence of detectable organic lesions, the build and

1. Stiller: Die Asthenische Konstitutionskrankheit.

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nervous construction of these individuals seemed to justify this conclusion.

The diagnosis of tuberculosis could not have been made in these cases on the usual symptoms and physical signs of this disease because these were absent.

These patients had no cough (with two or three exceptions), little or no fever, no night sweats, no hemophthisis, no rapid loss in weight, no sputum—hence no tubercle bacilli in sputum.

The presence of a tuberculous lesion in these cases was determined on, first, by a positive reaction to a subcutaneous injection of tuberculin. All the cases except one were injected and gave a positive reaction. In this case (Case 15) tubercle bacilli were subsequently found in the sputum. Second, a history of exposure to an open case of tuberculosis (nine of the fifteen gave this history). Third, doubtful lung signs not sufficient in themselves to establish the diagnosis but valuable as corroborative evidence (six of the fifteen cases gave these).

Roentgen-ray chest examinations were made in six of the cases; in four the roentgenologist reported positive findings in the lungs, in two negative. In one of the cases (Case 12) the roentgenologist reported a healed lesion. The patient, however, gave a positive reaction to tuberculin. In a second case (Case 11) the roentgenologist was in doubt ("diagnosis indeterminate: possible very early incipient tuberculosis"). Yet the patient reacted to tuberculin.

CLINICAL SYMPTOMS

The clinical symptoms of which the patients complained were varied and failed to conform to the symptomatology of any known organic disease. The non-conformity of the symptom complex is a characteristic feature of the cases. Hence the usual diagnosis of neurasthenia.

Named in the order of their frequency they are indigestion (10 cases), headache (9), constipation

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(7), loss in weight (7), cold hands and feet (6), mental depression (6), crying spells (5), physical tire (5), neckache (5), backache (5), general weakness (5), mental tire (5), worrying over trifles (4), eyeache (4), dysmenorrhea (4), insomnia (3), pains in the chest (2), voice tire (2), dizziness (2), tendency to take deep breaths (2), clearing of throat (2), palpitation of heart (1), shortness of breath (1), fainting spells (1), jerking of limbs (1). Only four had cough and in only one of these was there sputum coughed up.

A careful study of the symptoms complained of gives one no help in differentiating these cases from so-called neurasthenia. The symptom complex they present is the symptom complex described by all writers for so-called neurasthenia. It is the symptom complex diagnosed by all clinicians as neurasthenia. It is so-called neurasthenia.

DURATION OF SYMPTOMS

The symptoms in this group of cases were suffered from over a long period of time. The duration of complaints is measured in years rather than months or weeks.

Five were sickly from childhood. Three complained of symptoms five years or over; four from one to two years, while only three of the fifteen dated their complaints back less than one year.

These patients apparently possess a high resistance against the tubercle bacillus: a relative immunity given to them by tuberculous ancestors or by an infection contracted in childhood which the cell forces of the body have reduced to a quiescent state. If this were not so there would be more active recognizable tuberculosis and less so-called neurasthenia.

In many of them the tuberculous process never becomes very active; the bacilli are probably finally killed out and the individual in later life comes into a fair degree of health.

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In some active symptoms and signs appear only after years of suffering from the slow fires of a low-grade tuberculous toxemia often interpreted as neurasthenia (Case 15).

PHYSICAL FINDINGS

The physical examination of these patients revealed little or no positive evidence of organic disease.

In none was a positive clinical diagnosis of tuberculosis made. A searching examination of the chest and other organs was negative for tuberculosis or other organic disease in nine of the fifteen cases.

In the remaining six, doubtful physical signs in the chest were present; but in none of these were the findings fixed and definite enough to establish a diagnosis of tuberculosis beyond a reasonable doubt, even after weeks of observation.

In the majority of these patients the tuberculous process will go unrecognized or diagnosed as (so-called) neurasthenia if the clinician relies on the knowledge furnished him by physical examination alone.

PHYSICAL BUILD

Eleven of the individuals in this group were tall and slender. They had prominent, angular features; high cheek bones; long chests; long, flat or scaphoid abdomens, and slender arms and legs. Two were short of stature but slender build. Two others were of short, chunky build with round faces, broad full chests and short rounded abdomens, and short extremities.

All were of high-strung nervous temperament. All those (seven) in which the position of the abdominal organs was determined showed enteroptosis. Thirteen of the fifteen cases therefore conform to the physical construction of the "habitus phthisicus."

Stiller expresses the relationship between "habitus phthisicus" and "habitus asthenicus" in these words: "There is no doubt to my mind that the habitus phthisicus and habitus enteroptoticus are not only

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strikingly similar to each other but also are completely identical."[2] This study tends to confirm his conception.

TEMPERATURE

Ten of the group showed at times slight rises in temperature (99.2 to 99.4) usually in the afternoon with a subnormal morning temperature of (97 to 98.2). (Temperature records were taken with patients in bed.)

The afternoon rise would usually occur only occasionally, patients often going for days with no rise above normal. The subnormal morning temperature was more regular, most of the cases showing it day after day.

If these patients are up and about, however, they usually run a temperature of 99.2 to 100 under physical exertion or mental excitement.

These occasional temperature rises in persons with so-called neurasthenia are of great significance. They are often the only tangible clinical evidence of a concealed tuberculous lesion.

In this connection it is interesting to note that in Weir Mitchell's "Fat and Blood," every case reported by him (eight in all) in which systematic temperature records are given had fever (99.2 to 101.2).

PULSE-RATE

The pulse-rate in this group is characterized by its variability and its tendency to rise above the normal. The maximum was usually 100, the minimum about 70. In three cases the pulse-rate ran between 100 and 120. In two the minimum was as low as 60.

A variable pulse-rate is encountered in so many other organic conditions that its value from a diagnostic point of view is doubtful.

If, therefore, one were to draft a clinical picture of this condition with which we are dealing he would describe it as follows:

2. Es ist mir unzweifelhaft dass der Habitus phthisicus und enteroptoticus nicht nur einander auffallend ähnlich sondern ganz und gar identisch sind.

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A person usually under 25 years of age with or often without a history of known exposure to tuberculosis comes complaining of a varied lot of symptoms expressing nervous and physical exhaustion, the most common of which are indigestion, headache, constipation, mental depression, cold hands and feet, backache, neckache, eyeache, crying spells, chilliness, loss of weight, etc. These symptoms have dated back over a number of years with periods of improvement followed by relapse under unusual nervous or physical strain. Partial or complete breakdown often results.

On inspection one notes a poorly nourished, high-strung person with angular features, high cheek bones, long chest and abdomen, slender arms and legs and active reflexes.

A careful physical examination reveals no positive evidence of organic disease. Enteroptosis is usually present. Doubtful lung signs are occasionally encountered. The pulse-rate is usually increased; the temperature record shows an occasional afternoon rise to from 99.2 to 99.4 or more. The laboratory findings are negative for organic disease.

The clinician is puzzled; the long history, the build and nervous construction of the individual, the absence of the signs of organic disease leads to the diagnosis of neurasthenia (so-called). But what is this disease called neurasthenia? Will some one please answer?

Are these patients negative for organic disease? I have given the historical summaries of fifteen in which the evidence is positive that a tuberculous infection exists. It is an active tuberculous process because I do not believe that any one will be so foolish as to argue that a positive reaction to a subcutaneous injection of tuberculin means anything less than an active tuberculous process somewhere in the individual giving that reaction.

The location of the lesion whether it be in the lungs, lymph-glands, peritoneum, bones, or wherever it may be focused need not concern us at present.

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The fact stands out that in many of these individuals whom we have been considering negative for organic disease the evidence is incontrovertible that an active tuberculous infection does exist. Are we justified in taking the view that these symptoms of (so-called) neurasthenia are a clinical expression of such an infection? I think we are.

First, because we have no evidence to prove that these individuals harbor any other organic disease except tuberculosis.

Second, because we have good evidence for believing that tuberculosis is a chronic disease often contracted in childhood and remaining in the body in a semiquiescent state for years. The long history of many of these cases can thus be accounted for.

Third, because tuberculosis is the one chronic disease which gives most typically the symptoms of nervous and physical exhaustion encountered in neurasthenia (so-called).

Fourth, because we know that the tubercle bacillus produces a toxin (tuberculin) which circulates in the blood and is capable of producing for years a low-grade toxemia with all its varied clinical expressions.

Every experienced clinician marvels at the varied symptomatology of his recognized cases of tuberculosis, to say nothing of the clinical manifestation of those not recognized.

Are the cases presented patients with neurasthenia harboring an associated tuberculous process? I think not. If some one will demonstrate a pathologic base for neurasthenia so that it can be identified and differentiated from other diseases of known pathology, discussion on this phase of the subject might be profitably continued. In the absence of such pathologic lesions and with reliable proof of the existence in these individuals of a tuberculous process and of this only, it is only reasonable to conclude that an infection is present which is common and about which we know a great deal rather than with a name given to a symptom complex about which we know nothing.

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A further question immediately presents itself. What proportion of the cases diagnosed as neurasthenia in which a careful physical examination reveals no tuberculosis, no lues, no nephritis, no exophthalmic goiter, no gastric ulcer or any other recognizable organic disease, shows evidence of a concealed tuberculous infection? I have not as yet sufficient clinical data at hand to answer this question. In my experience, after excluding all other organic diseases, the number of persons exhibiting the symptoms of so-called neurasthenia failing to react to a maximum dose of a subcutaneous injection of tuberculin is small.

But is it not probable that if one were to select a given number of individuals and subject them to the subcutaneous tuberculin test as large a proportion would react as have reacted in this series of cases?

To this question I answer: No. In between 500 and 600 individuals with symptoms suggestive of a tuberculous infection whom I have injected with tuberculin for diagnostic purposes during the last twenty years, not more than 55 per cent. have given a positive reaction.

I have presented no distinctly pathologic proof that a tuberculous lesion exists in these individuals. This is impossible. These patients are living. They may not die for years. When they do die and are examined of what value is the evidence? If a tuberculous lesion were present at necropsy how could one know whether it existed at the time the individual complained of his symptoms. If a tuberculous lesion is present and healed how can one know whether it was healed at the time of the patient's illness. It it is present and active how can one know whether the lesion was present and active at the time the patient complained of his nervous and physical exhaustion?

Post-mortem evidence has proved the reliability of the subcutaneous tuberculin test, and farther than this need not be called up in settling the question under consideration.

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Nor can one rest his proof on the later development of recognizable tuberculous lesions. Some of these patients have already developed clinical evidence of the infection. Most of them have not and probably never will develop clinical tuberculosis as it is now understood.

The lesion is too minute, too well walled off, the bacilli are not virulent enough, or the resistance of the individual is too high.

It is for this very reason that so many of these cases are overlooked. It is for this very reason that the diagnosis of neurasthenia has so often been made.

Nor can the proof rest on the presence of tubercle bacilli in the sputum or other excreta. Most of these patients had no cough, hence no sputum and no tubercle bacilli in sputum.

A positive von Pirquet test was present in all but one case (Case 8). But a positive von Pirquet test can not be depended on to detect an active tuberculous infection. In this connection Case 8 is of interest. The von Pirquet test was negative while the subcutaneous test was positive. In my experience with between 500 and 600 injections of tuberculin for diagnostic purposes, I have met a number of cases in which the von Pirquet test was negative while the subcutaneous tuberculin test was positive. I shall make these cases a subject for a later study.

The stereoscopic Roentgen studies of the chest in the hands of an expert can be made of assistance in detecting some of these cases, but cannot be relied on in determining the broad question whether an active tuberculous process exists in these individuals.

The recognition of an active tuberculous infection in these cases must therefore rest primarily on a specific test (for this purpose I have used a subcutaneous injection of tuberculin), and secondarily on corroborative evidence such as a history of exposure to tuberculosis, or the presence of suggestive clinical evidence in the lungs, lymph-glands or elsewhere in the body.

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I have here presented evidence, which it seems to me is conclusive to prove that:

1. Many individuals exhibiting the symptom syndrome of so-called neurasthenia harbor a tuberculous infection and this only.

2. The tuberculous process in most cases is so concealed as to escape detection by the usual clinical examination methods employed, and a specific test must be used to reveal its presence.

3. In the light of this evidence these cases should be diagnosed as tuberculosis and not neurasthenia.

4. We should recognize and adopt a new clinical symptom type for concealed tuberculosis.

5. This symptom type is the symptom complex now recognized by clinicians the world over as neurasthenia.

REPORT OF CASES

CASE 1.—Miss E. L., aged 23, single, living at home, admitted to the St. Barnabas Hospital, Oct. 14, 1913, complaining of backache, insomnia, spells of depression, indigestion. Family history negative.

Present history includes a long series of ailments of various sorts, curvature of spine at 5 years of age, at first thought to be tuberculous, later considered hysteric; chorea at 10 years of age; dysmenorrhea at 15 years of age; various abdominal operations finally terminating in hysterectomy in February, 1912. No cause given by the operating surgeon for the hysterectomy other than that he considered it best for the patient's general state of health. No pathologic lesions found.

History of present complaints dates back over a number of years and includes a long series of symptoms, including indigestion, vomiting, abdominal pain, pain in back, insomnia, constipation, attacks of mental depression with hysteric manifestations, crying spells, dizziness, aching in the neck, headache, eyeache and physical tire on exertion. Has had a slight nervous cough for years. Patient has lost about 15 pounds in weight in the last year. Has dieted to such an extent that she can scarcely eat solid food of any kind.

Patient is a tall, angular-looking girl, high cheek bones, long chest and abdomen, marked tremor upper eyelids, increased knee-jerks, pupils react to light and accommodation, no incoordination, some tremor of finger-tips, no enlarged thyroid, no exophthalmos. Patient presents the stigmata of a highly nervous girl; hands, arms and legs were constantly twitching during examination; seems melancholy and

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depressed. Careful physical examination of this patient, including searching examination of the lungs, revealed no evidence of organic disease. There was gastroptosis, a dislocated kidney on right side, tenderness over abdominal aorta and along lower spine. Urine and gastric examinations negative, no occult blood in stools. Blood examination showed slight secondary anemia (hemoglobin 87 per cent.). Wassermann reaction negative. Von Pirquet test positive.

Patient was carefully observed in hospital over a period of two weeks. She had an occasional rise in temperature to 99.2. Pulse 85 to 100. She presented all the earmarks of a highly neurotic young woman, with frequent crying spells, much mental depression, vomiting attacks, insomnia. Complained much of cold hands and feet, backache, headache, and slight dry cough. No sputum. Had two fainting spells while going to the bath room. Roentgen examination of spinal column and lungs negative.

On the fifteenth day after admission, patient was given 1/20 c.c. of Bureau tuberculin,[3] showing a positive reaction (temperature 102) within sixteen hours after the injection. Following the positive tuberculin reaction the clinical diagnosis of neurasthenia was abandoned and the diagnosis made of tuberculosis (concealed), focus not determined, with chronic tuberculous toxemia exhibiting so-called neurasthenic symptoms.

Case 2.—Mrs. J., aged 37, married, one child. Family history negative for tuberculosis. Personal history negative except a miscarriage one year ago. Patient has been a healthy woman until one year ago when, following her miscarriage, she began losing in strength and weight.

Contracted la grippe about nine months ago which left her with a slight clearing of throat which continued for two months or more. This disappeared during the summer but reappeared again in the fall. No sputum coughed up. For the last three months has felt nervous and miserable; everything no matter how trifling seems like a mountain to her; she cries at the slightest provocation; is despondent and blue. The slightest exertion, mental or physical, tires her and she has had to give up all her social duties and home cares. Is bothered much with aching in the back of neck. Has had her eyes fitted repeatedly for glasses to relieve her headaches. Has cold hands and feet. Has had no pains in the chest. Appetite is poor. Has lost 10 pounds in weight in

3. Bureau tuberculin is the tuberculin made by the U. S. Bureau of Animal Industry. It is a 10 per cent. solution of Koch's old tuberculin. It is the tuberculin used in testing cattle for tuberculosis.

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six months. Patient had been carefully examined by different physicians who told her she was nervous and should take a rest cure.

Patient is a short, stockily-built woman, with broad chest and short abdomen, dark hair and eyes. Mucous membranes rather pale. Well-nourished. Weeps during examination. Pupils react promptly to light and accommodation. Knee-jerks active. Marked tremor of eyelids with eyes closed. Active dermatographia. Pulse rapid, 120 to minute. Temperature at office 99.4. No exophthalmos. No von Graefe's sign. Some tremor of finger-tips.

A searching physical examination was negative for organic diseases except that in the lower right chest anteriorly over the fourth and fifth interspaces a fine pleural friction-rub could be heard. Repeated examinations always disclosed the friction-rub in this area.

Urine and blood examinations negative. Wassermann reaction negative. Von Pirquet test positive. Not being able to make a positive diagnosis the patient was given 1/25 c.c. of Bureau tuberculin and gave a positive tuberculin reaction (temperature 100.4) within eighteen hours after injection was given. No Roentgen examination of chest made. The diagnosis of neurasthenia was then abandoned.

The friction-rub in right chest and the positive tuberculin reaction justified the diagnosis of tuberculosis of right pleura; chronic tuberculous toxemia exhibiting symptoms of so-called neurasthenia.

Case 3.—Mrs. L. W. B., aged 30, married, no children. Family history negative except one brother dead of tuberculosis. Personal history negative except childhood diseases. Well as a young woman, never had been sick. Married three years and has been occupied with her husband (a college professor) in teaching work.

About one year ago began running down in weight. At that time was spending many hours in the classroom and doing much outside church and social work. Became blue and depressed; cried easily and on slightest provocation. Was tired all the time and could not get enough sleep. Had an aching pain in back of neck, especially when tired. Also had headaches. Lost her appetite. Chilled easily; hard to keep her hands and feet warm. Had a slight cough, especially when using her voice much. No sputum. Hoarsed up easily after talking. Had no fever, no night sweats. Became so nervous and worn out that she had to stop teaching. Consulted various physicians who told her she had neurasthenia and was overdoing.

Patient is a tall, well-developed woman, some pigmentation of skin over cheeks and face. Long chest and abdomen. Face round and full. Patient is much depressed and weeps during the taking of the history. Knee-jerks very active;

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active dermatographia; pupils react to light and accommodation. Some tenderness in neck and along spine and over abdominal aorta.

A careful physical examination was negative for organic disease. There was gastroptosis. Urine and blood examinations were negative. No sputum. Pulse 95. Temperature showed an occasional afternoon rise to 99.2. A searching physical examination of the lungs was negative, except roughened breath-sounds in left apex. No impairment of percussion note. No râles heard. Von Pirquet test positive. No evidence of lues.

While under observation patient seemed a nervous, much depressed woman, cried at times and complained of aching pains in the head, neck, back, chest and limbs. On the fifth day a subcutaneous injection of 2 mg. of Koch's old tuberculin was given with a marked positive reaction (temperature 102.8) within sixteen hours following injection. No Roentgen examination of chest was made.

The diagnosis of neurasthenia was not confirmed. The diagnosis was made of tuberculosis (focus concealed) with chronic tuberculous toxemia exhibiting symptoms of so-called neurasthenia.

Case 4.—Mrs. W. V., aged 23, married, housewife, one child, referred to the University Hospital June 2, 1913, complaining of headache, dizziness, indigestion, backache, irregular and painful menstruation, and tenderness in the lower abdomen; symptoms dating back two and one-half years. Family history negative. Previous history negative, except whooping-cough as a child.

The patient was carefully studied for sixty-three days in the surgical service of the hospital and then referred to the medical service with the diagnosis of neurasthenia. After her transfer the patient was again examined. She was a tall, rather poorly nourished woman, high cheek bones, long chest and abdomen, color slightly anemic, active dermatographia.

A careful thorough examination including urine, blood and Roentgen-ray chest study revealed no evidence of organic disease. Wassermann reaction negative. Von Pirquet test positive. The patient exhibited the earmarks of a highly neurotic woman, and the provisional diagnosis of neurasthenia was concurred in. Pulse 60 to 90. Temperature normal with an occasional rise to 99.4 in the afternoon.

On the twenty-fourth day after admission to the medical service patient was given $\frac{1}{20}$ c.c. of Bureau tuberculin with a typical positive reaction within twelve hours following the injection (temperature rising to 101.6).

The diagnosis of neurasthenia was abandoned. The presence of a positive tuberculin reaction justified the diagnosis of concealed tuberculosis, focus not determined; chronic tuberculous toxemia exhibiting the symptoms of so-called neurasthenia.

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Case 5.—Miss I. P., aged 24, Scandinavian, single, white, housekeeper, admitted to the University Hospital Oct. 26, 1913, complaining of shortness of breath, headaches, precordial pain, lassitude and weakness on physical and mental exertion.

Family history negative. Personal history negative except usual childhood diseases. The patient was treated five years ago for neurasthenia and took a rest cure in a hospital. Her present complaints date back three months and includes a history of mental and physical tire, some loss in weight, headaches, especially when she reads, poor appetite and indigestion.

Patient is a tall, fairly well-nourished girl, high cheek bones, long chest and abdomen, fair color, pupils react to light and accommodation, knee-jerks active.

A thorough clinical investigation of this case, including pelvic and rectal examinations, also urine, blood and gastric studies, was negative for organic disease. No sputum. Wassermann reaction negative. Von Pirquet test positive. Temperature normal with an occasional rise to 99.2. Pulse 70 to 96. Clinical diagnosis based on the history of physical and nervous exhaustion with negative physical findings was neurasthenia with astigmatism (Macnie).

On the thirty-first day after admission patient was given subcutaneously 1/60 c.c. of Bureau tuberculin with a typical positive reaction (temperature rising to 101.4) within twenty hours after injection of tuberculin. The diagnosis of neurasthenia was then abandoned.

The history and the positive tuberculin reaction in the absence of evidence of other organic disease justified the diagnosis of concealed tuberculosis, focus not determined; chronic tuberculous toxemia exhibiting symptoms of so-called neurasthenia.

Case 6.—Miss H. W., aged 21, single, white, stenographer, admitted to the University Hospital, Jan. 28, 1913, complaining of pains in abdomen, indigestion, dysmenorrhea and nervousness.

Family history negative except that mother died after five months' illness of probable tuberculosis of lungs. One sister now has chronic cough. Patient has never been strong, long history of backaches, menstrual troubles and recurring winter colds. In July, 1911, had a nervous breakdown followed by a period of weakness and prostration. Finally became so weak and run down that she had to stop work.

Present complaint dates back over two years and consists of a long history of ill-defined pains in upper and lower abdomen and left chest, associated with indigestion, eructations of gas, nausea, loss in weight, cold hands and feet, painful menstruation, prostration and weakness.

Patient is a fairly well-nourished young woman, seems weak and talks in a low voice; long chest and abdomen;

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color good; pupils react to light and accommodation; knee-jerks active; palpable postcervical lymph-glands.

A careful thorough physical examination of this patient, including repeated examination of the lungs, revealed no positive evidence of organic disease.

The apex of the right lung was questionable; there was marked visceroptosis; blood and urine negative; there was no sputum; von Pirquet test was positive; Wassermann test not made. Temperature normal. Pulse 70 to 100. No positive diagnosis could be made. The patient was high-strung and nervous and this fact together with the negative clinical findings led to the diagnosis of neurasthenia.

On the thirteenth day after admission patient was given 1/20 c.c. of Bureau tuberculin subcutaneously with a typical positive reaction (temperature 100.4) within sixteen hours.

Roentgen examination of chest twelve days later showed "diffuse infiltration of both lung fields, especially marked in the right" (Bissell).

The diagnosis of neurasthenia was therefore abandoned and the diagnosis made of pulmonary tuberculosis with chronic tuberculous toxemia exhibiting symptoms of so-called neurasthenia.

Case 7.—Miss M. L., aged 32, single, stenographer. Father died of tuberculosis of the lungs, four sisters and one brother dead of tuberculosis of the lungs. Never strong as a girl, subject to colds and bronchitis. Three years ago was in California for bronchitis one winter during which she gained 12 pounds in weight. Gives a long history of ups and downs with weakness, poor indigestion, exhaustion from physical effort, aching in the back and loss in weight.

Comes now for pains in her right chest and precordial region which she has had for about a week. Has had pains also in the left chest for a month or more. Pains are a dull ache, and chest is sore to pressure. Occasionally patient feels pains in axillae, left scapula and back. Deep breathing or cough does not aggravate them.

For about two years patient has had a clearing of her throat, more marked in the morning. Has lost 10 pounds in weight during the past year. Appetite is poor. Is bothered much with sleeplessness. Has pains at her menstruation, and now feels so weak and nervous that she has had to stop work.

Has been examined by many physicians and lung specialists, all of whom had suspected her of being tuberculous, but none of whom had been able to find evidence of tuberculosis in the lungs or elsewhere in the body and had, therefore, diagnosed her case as neurasthenia.

Patient is a fairly well-nourished girl, looks high-strung and neurotic, color pale, light hair and eyes, high cheek bones, long chest and abdomen, pupils react to light and accommodation, tremor of finger-tips, knee-jerks active.

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A careful physical examination of this patient revealed no evidence of organic disease. A searching physical examination of the lungs was negative for tuberculosis. Patient had a moderate grade of gastroptosis. Sputum and urine examinations negative. Von Pirquet test positive. Blood-pressure 116. Pulse 90 to 100. Temperature normal.

Not being willing to accept the diagnosis of neurasthenia, and not being able to make the diagnosis of tuberculosis, the patient was subjected to an injection of 1/25 c.c. of Bureau tuberculin, and gave a positive reaction (temperature of 102) within eight hours after injection was given.

The clinical diagnosis of tuberculosis (concealed) with chronic tuberculous toxemia exhibiting symptoms of so-called neurasthenia was then made.

Case 8.—Miss L., aged 25, Jewess, single, stenographer. Family history negative except that mother died of tuberculosis when patient was a child at home.

Personal history negative except walking typhoid fever (?) five years ago. Operated on twice for pelvic displacements. Present history dates back six years and includes a long history of nervous symptoms, including headaches, backache, neckache, insomnia, cold hands and feet, indigestion, cough, exhaustion, rest cures, operations, treatment by osteopaths and Christian Scientists, etc. Insomnia and indigestion have been her most troublesome symptoms. Has been seen and examined by many physicians and the diagnosis of neurasthenia usually made. Has taken a number of rest cures from which she would temporarily improve and go back to work only to relapse into a weak, prostrated state, rendering her unfit for her occupation. Has lost 40 pounds in weight in the last six years.

Patient is an ambitious, intelligent, bright young woman, dark hair and eyes, high cheek bones, long chest and abdomen, slender limbs, pupils react promptly to light and accommodation, knee-jerks active, pulsating abdominal aorta, active dermatographia. Marked tremor of eyelids with eyes closed. No exophthalmos, no von Graefe's sign, no enlargement of thyroid.

A careful physical examination of this patient revealed no evidence of organic disease. There was marked gastroptosis and bilateral nephroptosis. Blood, urine and stomach examinations negative for organic disease. No Wassermann test made. Exploratory abdominal section negative for organic diseases in stomach, gall-bladder, appendix or elsewhere. Searching examination of lungs revealed no evidence of tuberculosis. Von Pirquet test negative. Temperature showed an occasional rise to 99. Pulse 80 to 100. The clinical diagnosis of neurasthenia seemed justified.

After patient had been under observation for six weeks and despite the negative von Pirquet, the patient was given

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1/25 c.c. of Bureau tuberculin with a typical positive reaction (temperature 101) within twenty-four hours following the injection.

The clinical diagnosis of neurasthenia was then abandoned and the diagnosis made of tuberculosis (focus concealed) with a chronic tuberculous toxemia exhibiting symptoms of so-called neurasthenia.

Case 9.—Miss S. (referred by her physician as a case of neurasthenia and admitted to Asbury Methodist Hospital, Dec. 1, 1909), aged 23, living at home, family history negative except that two sisters have died of tuberculosis of the lungs. Has never been a strong girl. Has always been very nervous and of late on account of a mental worry has been bothered with a constant desire to take deep breaths. This deep breathing occurs during the day while she is awake; is not aware of it at night (is present while the history is being taken). At times has a slight cough which has always been considered a nervous cough. No sputum coughed up. Has not lost in weight. Occasionally has slight fever (99.2). No sweats, no chills. For the last week has complained of feelings of distress in the upper abdomen.

Patient is a fairly well-nourished girl, sensible and intelligent, seems high-strung and fidgety, good color, long chest and abdomen, pupils react to light, knee-jerks very active, tremor of eyelids. During the examination patient keeps taking long deep breaths in rapid succession, one after the other. The deep breathing is worse when she sits up than when lying down.

A careful physical examination of this case including a searching examination of the lungs reveals no evidence of organic disease. Blood, urine and gastric contents normal. Von Pirquet test positive. The abdominal aorta was pulsating and tender and there was ill-defined tenderness over the upper abdomen, but no mass. Patient was repeatedly examined but no conclusion could be arrived at.

On the seventh day after admission patient was given 1/15 c.c. of Bureau tuberculin and gave a typical positive reaction with a temperature rise to 101.5 within fourteen hours following the injection. No Roentgen examination of the chest was made.

The diagnosis of neurasthenia was therefore not confirmed, but the diagnosis of concealed tuberculosis with chronic tuberculous toxemia producing neurasthenic symptoms was made. The focus could not be located.

Case 10.—W. K., aged 29, male, single, American, carpenter, referred to the University Hospital, Feb. 16, 1912, as a case of nervous dyspepsia and neurasthenia. Family history negative. No tuberculosis. Denies venereal disease. Has had mumps and small-pox.

Dec. 7, 1911, patient began complaining of palpitation of the heart. Consulted a physician who examined his heart

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and pronounced it all right. The attacks continued for a number of days until his stomach was washed out, since which time the palpitation has not bothered him. Patient has not felt well since the attacks in December. Is bothered with belching of gas after meals, constipation, headaches, especially at night, has felt weak and nervous, has frequent urination, and at times ringing in his ears. Patient has no cough. He has lost about 17 pounds in weight since sickness came on.

Patient is a thin, spare man, fairly well-nourished, color good, answers questions promptly and to the point, is nervous and apprehensive about himself. Pupils equal, react to light and accommodation, knee-jerks active, slight cyanosis of lips and finger-tips, cervical glands just palpable.

A careful physical examination of this patient revealed no evidence of organic disease, except a questionable area on the upper right chest anteriorly below clavicle. Here the percussion note is slightly impaired, expiration somewhat prolonged and a few fine cracking râles could at times be heard at the close of inspiration close to the right sternal border in first interspace. Blood examination showed a secondary anemia of mild grade. Urine and sputum negative. Von Pirquet test positive. Gastric analysis negative except an increased acidity. Pulse 60 to 80. Temperature 97 to 98.4.

On the tenth day after admission patient was given 1/20 c.c. of Bureau tuberculin with a positive typical reaction (temperature 102.0) within sixteen hours following the injection.

Roentgen examination of chest March 1: "There is a rather marked thickening about the hilus of the right lung. A number of peribronchial lymph-nodes in both lungs. The right apex is distinctly more dense than the left." Roentgen diagnosis: Incipient tuberculosis (Bissell).

The diagnosis of neurasthenia could not be confirmed. The suspicious physical signs in the chest, the positive tuberculin reaction, the Roentgen chest findings justified the diagnosis of tuberculosis of the right lung with chronic tuberculous toxemia exhibiting symptoms of so-called neurasthenia.

Case 11.—Miss E. G., aged 16, white, Irish, single, referred to the University Hospital, Sept. 22, 1913, complaining of loss in weight,, poor appetite, headaches, amenorrhea and insomnia. Family history negative. Father, mother and ten brothers and sisters living and well; one sister has a goiter.

Previous History: Whooping-cough, measles, mumps, and chicken-pox as a child; cervical glands of neck at 8 years of age which were operated on and removed.

The girl was fairly well until last April. She was studying hard at school and began having afternoon headaches. Aching would come on in the eyes and she would have to stop studying because of the eyeache. Was fitted with glasses but without relief. About this time she began having indigestion and was troubled with constipation. Finally

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had to go to bed and was in bed eight weeks because of weakness and headaches. Was also bothered with pains in her arms and legs, neuralgic in character.

In June felt a little better of her headaches, but felt tired and weak. Her appetite began to fail, she lost weight. In July the headaches started again, diffuse over whole head. These have kept up to the present time. Is bothered with pain at her menstrual period, which continues for one day after the flow starts. Has come to the hospital because of her headaches and weakness.

Patient is a fairly well-nourished girl of 16 years, dark hair and eyes, rounded full face, normal chest and abdomen, color good, pupils react promptly to light, knee-jerks present, marked tremor of eyelids with eyes closed. Seems nervous and high-strung. Tendency to take deep breaths, moving limbs from side to side, answers questions in a low voice, slight dry cough, teeth fairly good, old scars of operation on left side of neck, also a few pea-sized palpable lymph-glands.

A careful physical examination of this case revealed no evidence of organic disease outside of an area of impaired resonance in the upper right chest, posteriorly. No râles heard in this area. Slight increase of vocal fremitus. A soft blowing systolic murmur was heard over the second left intercostal space, and on exertion a soft systolic bruit was heard in the apex area which promptly disappeared on rest in bed. Blood examination negative; blood-pressure 110. Pulse 80 to 120. Temperature normal. Wassermann negative. Von Pirquet test positive. Urine 1,026, no albumin, no sugar, occasional hyaline cast. The history, the absence of evidence of well-defined organic disease lead to the diagnosis of neurasthenia.

On the seventh day after admission patient was given 1/25 c.c. of Bureau tuberculin subcutaneously and gave a typical positive reaction (temperature 101) within twelve hours following the injection.

Roentgen lung examination (Bissell): "Left third and fourth interspaces show slight mottling and network; diagnosis, indeterminate, possibly very early incipient tuberculosis."

The diagnosis of neurasthenia was then abandoned. The history of diseased glands in the neck in childhood, the Roentgen chest findings, the positive tuberculin reaction justified the diagnosis of tuberculosis of the lungs with chronic tuberculous toxemia.

Case 12.—G. H. G., aged 42, male, white, single, referred to the University Hospital, April 30, 1912, complaining of headaches, backache, exhaustion on exertion such as walking, pains in stomach, and loss of appetite. Diagnosis of referring physician was neurasthenia. Family history negative, except that father died of quick consumption. Patient was at home at time of father's illness.

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Patient had mumps at 2 years, typhoid fever at 16 years and malarial fever at 34 years.

The history of his present trouble dates back eight years and consists of a long history of ill-defined, abdominal pains, constipation, headaches, cold hands and feet, aching joints, nausea, poor appetite and general weakness on exertion. Has not been able to work for two years. Has tried repeatedly but always played out. Very introspective. Talks in a low, feeble voice. No cough.

Patient is a rather poorly nourished man, color fairly good, high cheek bones, thin nose, long chest and abdomen, active knee-jerks, pupils react promptly to light and accommodation, active dermatographia.

A thorough physical examination including urine, blood and gastric studies, revealed no evidence of organic disease. There was marked gastroptosis. The urine contained a trace of albumin and an occasional hyaline and granular cast. No other evidence of nephritis. No arteriosclerosis. No enlarged heart. Blood-pressure 120. Wassermann was negative. von Pirquet test positive. Temperature 97.8 to 99.2. Pulse 80 to 104. Patient was kept in the hospital forty-five days and discharged much improved with the diagnosis of neurasthenia and nephritis (?).

Nov. 23, 1912, patient was readmitted with all the old symptoms of physical exhaustion and mental tire. Patient remained in the hospital fifty-six days and was again carefully studied. On the fourteenth day after admission patient was given a subcutaneous injection of 1/15 c.c. of Bureau tuberculin with a prompt positive reaction, temperature rising within twelve hours to 101.4.

Roentgen examination of chest: "A diffuse cloudiness throughout both lung fields, slight thickening of the bronchial tree and a few soft lymph-nodes. No active tuberculosis of lungs; the fibrosis is probably due to a former tuberculous process" (Bissell).

The diagnosis of neurasthenia was then abandoned and the diagnosis made of tuberculosis, focus not determined; chronic tuberculous toxemia; low-grade nephritis.

Case 13.—C. R., aged 24, male, single, tinner, referred to the University Hospital Feb. 14, 1912, from the University Free Dispensary with the clinical diagnosis of sexual neurasthenia.

Family history negative, previous history negative except diphtheria at 10 years of age, from which he recovered slowly. Admits masturbation and use of alcohol at times to excess. Denies venereal disease. Has always had a tendency to nervousness and headaches. At times gets weak and short of breath. Is often blue and despondent.

Present illness dates back about one month, came on with a sharp pain in the left chest over the heart while walking. Pain lasted four or five days, was worse on deep inspira-

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tion and extended up into left shoulder. Thinks he may have had some fever. No night sweats, no cough. Since the sharp pain has subsided patient has had a dull ache in the left chest. Has felt worried, nervous and weak since the pain came on; no loss in weight; appetite fair; bowels constipated.

Physical examination reveals a nervous, restless man of 25 years, tall build, long chest and abdomen, high cheek bones, very apprehensive, a fine general tremor passing over body from time to time as if he were shivering cold. Nutrition and color good. Pupils react to light. Knee-jerks active. No Romberg. Active dermatographia. No disturbances of sensation.

A careful thorough physical examination of this patient, including blood examination, was negative for organic disease. No sputum. Urine: specific gravity 1.025, trace of albumin, occasional narrow hyaline cast. Wassermann reaction negative. Von Pirquet test positive. Temperature 96.6 to 99.3. Pulse 72 to 96.

On the sixth day after admission patient was given 1/15 c.c. of Bureau tuberculin subcutaneously and gave a typical positive reaction (temperature to 100.4) within twelve hours following the injection.

Following the reaction to tuberculin the patient's lungs were more carefully examined and an area of impaired resonance discovered in right chest anteriorly below right clavicle. No râles heard in this area.

The diagnosis of neurasthenia was then abandoned and the diagnosis made of concealed tuberculosis, focus not determined (probably in upper right lung), with chronic tuberculous toxemia.

Case 14.—Miss S., aged 23, single, living at home, good family history except that two sisters died of tuberculosis. Previous history reveals no serious diseases. Has never been a very strong girl and has always tired easily. Has had a slight nervous (?) cough for years, never coughed up any sputum. No loss in weight.

Consulted her physician ten days ago for indigestion, with pains in upper abdomen after meals. At this time she began to be bothered with her breathing and was impelled constantly to take deep breaths. She felt very nervous and did not sleep well. No vomiting, no belching of gas. Bowels were constipated.

On examination one notes a well-nourished young woman of good color, thin and tall, answers questions promptly and intelligently, has a slight dry cough, more like a clearing of the throat, coughs up no sputum. Pupils react to light and accommodation, knee-jerks active, marked tremor of eyelids. During the examination patient keeps taking one long deep breath followed by two or three short superficial inspirations, and then another deep full breath. This is worse

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when she sits up than when lying down. When asked why she does this she says it gets air into her lungs. Patient's limbs are constantly twitching and jerking. Seems much depressed and weeps during the examination.

A careful physical examination of patient revealed no evidence of organic disease. Abdominal aorta pulsates and is tender to touch. Searching examination of lungs was negative for tuberculous lesions. Temperature showed an occasional rise to 99.4. Pulse 90. Urine and blood examinations negative. Von Pirquet test positive.

Patient presented all the earmarks of a highly nervous girl and the diagnosis of neurasthenia seemed justified.

On the eighth day after admission to the hospital, patient was given 1/15 c.c. of Bureau tuberculin, and gave a positive typical reaction (temperature rise 101.2) within twenty-four hours following the injection.

The diagnosis of neurasthenia was then abandoned and the clinical diagnosis changed to tuberculosis (focus concealed) with chronic tuberculous toxemia exhibiting symptoms of so-called neurasthenia.

Case 15.—Mrs. E. T. L., aged 32, married, two children, family history negative except that one sister had died of tuberculosis. Patient was at home at the time of the sister's illness.

Patient was never very strong as a child, but grew to maturity without serious illnesses, and was fairly well until after the birth of her first child six years ago. At that time recuperated slowly and was bothered much with nervous depression, indigestion, backache and neckache. Ever since that time patient has had to be very careful of her strength. The slightest unusual mental or physical exertion tires her. Cannot read without headaches. Entertaining friends at dinner sends her to bed exhausted. If she eats under excitement or in a hurry is bothered with much belching of gas. Has a persistent aching in the back of her neck which is worse whenever she overdoes. Voice tires easily and becomes hoarse if she talks much. Has a persistent clearing of her throat which is worse when she is tired. Is good for nothing most of the time, discouraged and blue because she cannot do what other women do. Her children annoy and tire her. She worries over trifling annoyances in her home life, all her small household cares seem like mountains to her. Even visiting with her friends leaves her with a nervous, weak feeling. Still she keeps up and drags herself about. She is sensitive to changes in temperature and bothered with cold hands and feet. Has been seen and treated by various physicians for neurasthenia.

Physical examination reveals a rather tall, intelligent woman, fairly good color, light hair and eyes, high cheek bones, is nervous and high strung, long chest and abdomen.

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Marked tremor of eyelids when standing with eyes closed. Active knee-jerks; pupils react to light and accommodation.

A careful physical examination reveals no evidence of organic disease outside of a pleural friction-click at the close of inspiration over the third and fourth interspaces on the left chest anteriorly. No râles heard in this area. No impaired percussion note. No fever. Pulse small, 95 to minute. Patient has a moderate grade of gastroptosis and a movable right kidney, readily palpable. Some tenderness over abdominal aorta. Urine, stomach contents and blood examinations negative for organic disease. Coughs up no sputum. Von Pirquet test positive. No subcutaneous tuberculin test made.

The long history of nervous symptoms, the absence of well-defined symptoms of organic disease and the negative laboratory findings led to the diagnosis of neurasthenia with a left-sided dry pleuritis.

Patient was placed on proper treatment for her physical and nervous exhaustion and improved steadily, but after a time an occasional fine crackling râle could be heard at the tip of the left apex, anteriorly and posteriorly. The râles appeared and disappeared. Were not always present. Finally, after patient had been under observation a number of months, a small quantity of sputum was secured which contained tubercle bacilli.

The diagnosis of neurasthenia was then abandoned and the diagnosis made of tuberculosis of the apex of left lung; tuberculosis of left pleura; chronic tuberculous toxemia exhibiting symptoms of so-called neurasthenia.

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ABSTRACT OF DISCUSSION

Dr. Nathan Rosewater, Cleveland: Dr. Head is right in distinguishing these cases of disguised starvation from neurasthenias. I believe a much larger class which have "that tired feeling" in the morning after sound sleep are obviously not neurasthenias, since the neurasthenic class after a night of rest with sleep wake up refreshed from the rest of nerves, brain and body, and only as they tire out sooner or later do they fag. Another class described in the paper which I read before this Section in 1908 as cases of "disguised starvation" should also be excluded. These are cases of more or less undernourishment resulting in more or less bankruptcy of brain, muscles, organs or tissues with impoverishment of circulatory fluids, which condition is perhaps the greatest cause of non-resistance to tuberculosis or other germ invasion, because neither the blood-stream nor the exhausted cells are in any condition to offer the necessary 100 per cent. or more of resistance to the invading germs from without, nor are they able to

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prevent the breaking down of foci already present. A class akin, is of those who wake refreshed but complain of wearing out before or soon after noon, unable to keep brain and body at work. On questioning these we find that they have taken for breakfast a cup of coffee, with or without a little bread. This insignificant meal cannot prevent the human machine from breaking down, any more than an automobile can be kept going when one starts away with a pint of gasoline instead of five gallons. These patients when advised to eat three or four eggs for breakfast come back reporting that they are veritable indefatigable steam-engines. Tuberculin may give a positive reaction in nearly all cases in adults but that does not prove active tuberculosis. A woman patient suffered from insomnia, but was otherwise well. Roentgenograms were made and she was told she had pulmonary tuberculosis, basing it on the Roentgen-ray findings and rapid pulse. She had neither fever, cough, râles nor other symptoms. She was examined by three abler men than myself and no active tuberculosis found. This was nearly five years ago and she is still in excellent health. As to the enteroptoses, they may be primary or secondary, mostly the latter. I have seen many with nephroptosis, gastroptosis, etc., some with Stiller's habitus and quite a number without. These ptoses are due to asthenias, occurring before or after the development of the habitus, and caused primarily by a large variety of undermining, exhausting influences, metabolic, toxic, infectious, psychic, or by overstrain or underfeeding, and not until the primary causes and the ptoses are overcome will these secondary asthenias respond to treatment.

Dr. F. M. Pottenger, Los Angeles: Dr. Head has illustrated the important fact that neurasthenia has a tuberculous toxemia as an underlying cause in a large percentage of cases. Tuberculosis affects all of the systems of the body, and, strange to say, even the symptoms of the early pulmonary form of the disease calls the attention away from the lungs rather than to them, the larynx, the heart, the stomach and the nervous system seemingly being affected. This neurasthenia is better understood when we recall that tuberculosis begins in childhood; that nearly every individual is affected; that the lesion heals in some at once, but in many passes through stages of quiescence and activity, extending now and then from the primary focus of infection to other parts of the body, so that necropsies in adults show more than 50 per cent. in and about the apices of the lungs. From such lesions as fail to heal, toxins are given off which have a profound effect on the nervous system, producing neurasthenia. Many young people who fail to develop properly, who have lowered resistance and manifest an unstable nervous system belong to this group. Such patients often

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respond remarkably well to the measures used in the treatment of tuberculosis and are definitely benefited by tuberculin treatment. Many believe that the phthisical habitus is often a result of tuberculosis instead of a cause. Unless the medical profession can get away from their conception that tuberculosis is the disease which we usually term consumption, and will recognize the early infection and the slight symptoms which are produced months, sometimes years before the active advanced stage manifests itself, it will miss completely the point of the modern teaching concerning this disease.

Dr. Charles Stover, Amsterdam, N. Y.: Myasthenia gravis should be differentiated before determining that the patient is suffering from neurasthenia. It is not uncommon, particularly among those who are interested in diseases of the nervous system, to meet both the neurasthenic and tuberculous type of cases which, in course of time, come under the classification of myasthenia gravis.

Dr. Eliza Mosher, Brooklyn: I have been much interested in the statement that nearly all of the patients included in Dr. Head's report had enteroptosis. According to Sir Arbuthnot Lane of London, intestinal stasis due to enteroptosis is one of the underlying causes of a large number of special diseases, tuberculosis among the number, and I believe he is right. We are finding behind many cases of neurasthenia, melancholia and even epilepsy, the systemic poisoning produced by the products of chronic intestinal stasis, and as we become skilled in the diagnosis of gastro-intestinal displacements, "bands" and "kinks," we shall more and more often find one or all of these conditions present in the abdomen of patients suffering in these and other ways. I also understood Dr. Head to say that in the cases he reported the long slender trunk so common among young tuberculous patients was a common feature. I have yet to find a delicately built girl of this type, especially if she has broad hips, who does not manifest a strong tendency to enteroptosis. Dr. Head's cases should arouse us all to the importance of making a careful examination of the abdomen in all of our patients and especially in slender-bodied undernourished, neurasthenic girls and women.

Dr. A. J. Caffrey, Milwaukee, Wis.: We all know that a very large number of neurasthenics pass through the free dispensaries, and I have charge of the medical department of the free clinics in the Marquette University at Milwaukee and have been making routine tuberculin tests of the patients we class as having neurasthenia. In nearly all cases, perhaps 90 per cent., there is a positive reaction to subcutaneous injections of tuberculin and also to the von Pirquet test. I think, from these observations, that there must be some

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direct connection between neurasthenia and concealed tuberculosis.

Dr. John Ritter, Chicago: I have observed that in at least 40 per cent. of the so-called neurasthenic patients, tuberculosis in some form is present. It, like walking typhoid, belongs to that large category of diseases in which more than 50 per cent. of patients are tuberculous. We see it in cases of hypo-acidity, of which at least 30 per cent. point to tuberculosis. All these, like tuberculosis following trauma, are manifestations of a previous existence of tuberculosis, the symptom-complex only following in the train of a previous disease. Tuberculosis is, as Dr. Pottenger points out, like syphilis and follows a similar course. The full picture of pulmonary tuberculosis is only the last or tertiary stage of the disease following long after the primary infection. I cannot too strongly emphasize that, in the use of tuberculin for diagnostic purposes, the intracutaneous mode of application should be used and not the subcutaneous. In the public schools in Vienna every child, at entrance, is given a von Pirquet test for diagnostic purposes. To all who do not react to this test a second one is given intracutaneously, and it has been observed that about 80 per cent. of those children who do not react primarily to the von Pirquet react positively to the Manteau test. With regard to the cases of healed lesions, the application of tuberculin for testing purposes is of no value because from the very nature of the diesase we know that these cases all react positively.

Dr. Tom A. Williams, Washington, D. C.: I cannot agree with Dr. Head's statement that all neurasthenia is due to latent tuberculosis. While I am one of the few neurologists who believe that neurasthenia, unlike psychasthenia and hysteria (which are psychogenetic), is a purely physical disorder and, moreover, due to some cause or other extraneous to the nervous system, rather than to hypothetic "nerve fatigue," I cannot accept latent tuberculosis as the sole source. We must remember that symptoms quite similar to those described by Dr. Head, are not uncommon, as every southern physician knows, in the early stages of pellagra, in hookworm disease and in latent malaria. Besides dysthyroidea as well as other glandular irregularities is responsible for disorders often labeled neurasthenic. In connection with Dr. Head's thesis, however, it is interesting to recall the investigation made in the neurologic clinic of the New York Postgraduate Hospital some years ago by Dr. Haskell, who found many of the neurasthenics suffering from a tuberculosis which had been overlooked by other physicians. Many of us regard enteroptosis not as the cause but as the effect of asthenic states, to which also the intestinal disorders may be secondary; furthermore, it must be

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remembered that many cases of enteroptosis develop neither neurasthenia nor tuberculosis. With these qualifications, Dr. Head's paper should be of the greatest value in warning practitioners against permitting themselves to make a diagnosis of neurasthenia.

Dr. Walter B. Swift, Boston: I agree with Dr. Williams that not all patients with neurasthenia have tuberculosis. A young woman in the neurologic service of the Boston City Hospital presented all the typical signs of neurasthenia. Six or eight months after that diagnosis was made she died of carcinoma of the stomach. Neurasthenia is not a useless word. It makes a good waste-basket—something to say in place of "I don't know." We would do better to dispense with not the word but the waste-basket and instead give these patients further exhaustive physical and mental investigation.

Dr. Albert Robin, Wilmington, Del.: Neurasthenia is a word rather loosely used to the great disadvantage of the suffering public. This term "neurasthenia" is now used as the term "malaria" was formerly used. The more we practice medicine the better diagnoses are made and we do not have to fall back on these terms of doubtful significance. In connection with my work at the tuberculosis clinic for the past ten years fully 20 per cent. of those applying for treatment have no other physical examination made except a casual one through the patient's clothing. I believe that neurasthenia is intimately associated with the early stages of tuberculosis, and because few men are able to make a diagnosis of incipient tuberculosis it is necessary to formulate some scheme by which a diagnosis in the early stages of tuberculosis may be arrived at. The busy doctor has not the time to make a thorough examination in these cases; in fact he hardly has the time to read his medical journals, and thus familiarize himself with latest methods. It should be remembered, in making a differential diagnosis between neurasthenia and tuberculosis, that in the former disease there is no elevation of temperature. In every case of tuberculosis or tuberculous toxemia, in these cases of concealed tuberculosis at one time or another there is a slight elevation of temperature. This temperature curve appears particularly after exercise. The question of exercise in making a diagnosis of concealed tuberculosis is one of great importance, and if patients are kept under observation for any length of time the diagnosis can be readily made. I am referring to slight exercises. I generally instruct the patient to walk to my office every evening, for a week, and I take his temperature immediately on arrival. A slight elevation of temperature will appear which will not appear at other times. I am in favor of an educational campaign among physicians that will cause them to be more careful in examining their patients

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in order to detect concealed tuberculosis or the disease in its earlier stages. I want particularly to emphasize the importance of detecting this elevation of temperature following exercise, which is as diagnostic as the reaction following injections of tuberculin, and far safer. The symptom-complex of neurasthenia plus slight elevation of temperature on exertion, plus rapid pulse, means tuberculosis.

Dr. J. P. Munroe, Charlotte, N. C.: In a paper which was read at the state society of North Carolina it was stated that the tubercle bacilli found in animals in the mountains were acid-stained and in every animal examined they were practically identical with the tubercle bacilli found in the human body. Also the symptoms appearing in these tuberculous animals were like those that appeared in the human being.

Dr. Robert N. Willson, Philadelphia: It would seem as though one were taking a rather radical step in endeavoring to include in the term "tuberculosis" all or even a large percentage of the cases of neurasthenia or nerve-tire. No one questions that the tuberculous toxin may and does predispose to neurasthenia in certain cases. Just as certainly there are many patients with neurasthenia who show no evidence during life of tuberculous infection, either before or after their cure. Most cured neurasthenics enter on their convalescence without any treatment directed toward or suitable to tuberculosis. Again, many cases of neurasthenia have a definite etiology that can be traced altogether distinct from tuberculosis, such as cardiac disease, intestinal toxemia, nervous overwork or worry, syphilis, oftentimes the very lack of a definite object in life and the consequent irritation and fretting of unsympathetic home surroundings. Neurologists speak of various types, sexual, cerebral, cerebrospinal, gastric and circulatory. Often these terms are more closely related to the etiology than to the symptomatology. Not one of the pictures is necessarily tuberculous. Of course any one may be, in a given instance. An important etiologic phase of the subject has been altogether neglected in the discussion, which would have been touched on at once had there been a thoroughgoing neurologist present. No one has mentioned the fact that practically every case of neurasthenia develops from neurotic and often from positively neurasthenic soil. We seldom fail to find the parentage of a neurasthenic tainted on one side or the other with nervous invalidism. Alcoholism, epilepsy, insanity, hysteria and neurasthenia are the progenitors of neurasthenia in the second generation. Tuberculosis may or may not be present as a concomitant, and perhaps as an exciting factor. When the soil is tainted, however, tuberculosis is not needed as a factor in the causation of the neurasthenia, which will

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develop in the child of the neurotic parent when the conditions are right.

Dr. George Douglas Head, Minneapolis: My contention is not that all cases of so-called neurasthenia harbor a latent tuberculosis, but that in the group of cases clinically diagnosed as neurasthenia, after excluding syphilis, heart-disease, exophthalmic goiter, gastric ulcer, nephritis and all other known organic diseases, a certain number remain in which no organic lesion can be found. This "remnant group" has been considered negative for organic disease, and because of the existence of these cases the clinical entity neurasthenia has been kept alive. Now when the individuals in this group supposed to be free of organic disease are tested with tuberculin, a large percentage of them show evidence of harboring an active tuberculous lesion, so concealed, however, as to escape detection by the usual clinical examination even of the most searching kind. I contend that the symptoms of nervous and physical exhaustion displayed by these patients and now diagnosed as so-called neurasthenia is in reality a clinical expression of a concealed tuberculous lesion and that we should recognize a new clinical symptom-type for concealed tuberculosis which is the symptom-type we now give to neurasthenia. The question has been asked, What percentage of the cases in this "remnant group" of so-called neurasthenias give evidence of harboring concealed tuberculous lesions? I am not prepared to answer this question at this time because my series of observed cases is not large enough to give reliable data. Roughly speaking, I should say that about 20 per cent. of the "remnant group" fail to give a reaction to a subcutaneous injection of tuberculin.

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THE USE OF ATOPHAN AND RADIUM EMANATION IN THE TREATMENT OF GOUT AND THE ARTHRITIDES *

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AND

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Medicine has long awaited a therapeutic agent which would induce a significant increase in the output of uric acid. Before the introduction of atophan, aside from the salicylates, there was no drug which could be relied on to bring about this condition. During the six years of its history, abundant data have accumulated demonstrating that atophan may increase the elimination of endogenous uric acid from 50 to 200 per cent., and the mechanism by which atophan acts has been the object of much investigation. Disregarding the several views held concerning this point, we may say that at present the simplest and most satisfactory explanation is to be sought in an increased permeability of the kidneys, by which the level of uric acid retention is lowered, thus permitting a draining of this substance from the blood and tissues. While there are occasional scattered data in the earlier literature on atophan which appear to favor this view, nevertheless the idea may be said to have received its first experimental support when Folin and Lyman,[1] by means of the Folin-Macallum colorimetric method, demonstrated an unquestionable decrease in the uric

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1. Folin and Lyman: Jour. Pharm. and Exper. Therap., 1913, iv, 537.

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acid concentration of the blood associated with the augmented output in the urine. These observations have since been confirmed by McLester,[2] Steinitz[3] and ourselves.[4]

Whatever may be its cause, gout is undeniably characterized by a concentration of blood uric acid which is from two to five times as great as that observed in normal individuals. Whereas, in the majority of normal individuals one finds 1 to 2.5 mg. uric acid per hundred grams of blood, in gout it is in general as high as 4 to 6 mg. Since the principle of treatment in gout is to avoid purin foods and to maintain the uric acid of the body tissues as low as possible, it would seem that an agent which is essentially a specific eliminant for uric acid, as atophan appears to be, would form a rational therapy in this condition. It then becomes desirable to learn the details attending the action of this drug.[5] We have found that the action of atophan on the blood uric acid begins to make itself felt within two or three hours after its administration, that is, as soon as absorption has taken place, and reduces the blood uric acid to a minimum concentration within about two days. This minimum concentration appears to vary for different individuals from 0.7 to 2.5 mg. per hundred grams of blood and cannot be further lowered even when the drug is administered continuously for a month and a half. The original level of uric acid concentration is nearly reattained after the use of the drug has ceased for two days.

Under treatment with atophan, all of the five cases of gout showed improvement of more or less permanence, as did also four cases of possibly gouty nature. Of the eleven cases of arthritis of various types, two showed some improvement. A superficial summary of

2. McLester, James S.: Studies on Uric Acid of Blood and Urine, with Special Reference to the Influence of Atophan, Arch. Int. Med., December, 1913, p. 739.

3. Steinitz: Ztschr. f. physiol. Chem., 1914, xc, 108; Deutsch. med. Wchnschr., 1914, xl, 953.

4. Fine and Chace: Proc. Soc. Exper. Biol. and Med., 1914, xi, 111.

5. For further details see Fine and Chace: Jour. Pharm. and Exper. Therap., 1914.

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clinical results of this character cannot, however, convey an adequate view concerning the value of the treatment. Thus, in one case of gout, there was almost immediate improvement after taking atophan, which persisted even after the cessation of the use of the drug, and in spite of the return of the uric acid concentration of the blood to the original level; while in another case of gout, the initial improvement became less pronounced in spite of the continued use of atophan and the maintaining of the blood uric acid at less than half its original level. We shall reserve a more careful analysis of the clinical results until we have had an opportunity to extend our observations over a longer period of time.

In contradistinction to gout, arthritis is not characterized by an excessive concentration of uric acid in the blood; and this difference, in our experience, has been of aid in distinguishing between these conditions. Thus in one case, which by several clinicians was regarded as typical gout, there was a constant uric acid concentration of but 2 mg. per hundred grams of blood. A careful investigation disclosed a colon bacillus infection in the pelvis of the kidney, which was cleared up under the administration of the appropriate vaccine, whereupon all "gouty" symptoms disappeared. We are not yet prepared to assert that a high concentration of uric acid is essential for a diagnosis of gout, but our experience with those cases of joint and muscle involvement associated with a uric acid concentration of less than 2.5 mg. has indicated the desirability of a diligent search for foci of infection in various parts of the body, which may be the primary cause of the joint affections.

The improvement noted in certain cases of arthritis can hardly be explained by an influence on the elimination of uric acid. The usual lowering of the uric acid concentration of the blood is indeed noted, but there is no reason to regard uric acid as a factor in the etiology or progress of arthritis. In such cases

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there appears to be an analgesic action, which may likewise to some extent account for the relief felt by gouty individuals.

With regard to the influence of radium emanation on uric acid metabolism, various European workers have emphasized essentially two points: the increased elimination in the urine and the reduction or disappearance of uric acid of the blood. The increased elimination of uric acid in the urine under the influence of radium emanation is perhaps due to the induced leukocytosis with subsequent leukolysis. In the light of recent developments in purin metabolism, the disappearance of uric acid from the blood as noted by Gudzent[6] is a most unusual observation. It has not been supported by beaker experiments or by our own studies.

We have thus far treated thirteen cases of gout and arthritis in an emanatorium with radium emanation of 0.5 to 150 Mache units per liter of air in one- to two-hour sittings for one to two months; two cases of arthritis with radium drinking-water; and five cases of arthritis with injections of radium bromid equivalent to 50 to 100 micrograms of the element. In no instance was there any change whatever in the uric acid concentration of the blood. In view of these findings we can hardly subscribe to Gudzent's claim that with concentrations of radium emanation of as little as 2 to 4 Mache units per liter, uric acid disappeared from the blood and remained absent as long as one year.

With regard to clinical effects, we may say that in only two instances—those in which radium solutions were injected—did there appear to be any improvement. Here again, however, we feel that the treatment should be extended over a greater interval, before conclusions can be properly drawn with regard to clinical results.

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6. Gudzent: Berl. klin. Wchnschr., 1911, xlviii, 2098.

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ABSTRACT OF DISCUSSION

Dr. Charles G. Stockton, Buffalo, N. Y.: With reference to the effect of atophan in relieving the uric acid burden of the blood we have given the drug in studies of the blood, including the method of Folin. The drug has acted unpleasantly in some instances, although usually it occasioned no trouble. One other question is what is commonly meant by the term gout. Dr. Chace spoke as though gout was a condition parallel to excess of uric acid in the blood, or uricacidemia. Gout is something in addition to an excess of uric acid in the blood. Just what that something is remains to be seen. In one case coming to my attention the patient had 25 mm. of uric acid in 100 c.c. of blood when not treated, but after long-continued dietetic treatment and the use of atophan he was discharged with 8 mm. of uric acid to 100 c.c. of blood, and yet he had no gout. He had had an attack of gout ten years before. At the same time I had two cases of gout under treatment, one patient having 5 and the other 7 mm. of uric acid to 100 c.c. of blood; one was treated by atophan and the other by colchicum and both by alkalies; the results were compared. I saw but little difference, save that the atophan seemed to have rather the better effect in reducing the uric acid. The clinical course of the two cases was much alike, both having been severe and typical gout.

Dr. S. Solis Cohen, Philadelphia: For a number of years I have been making use of atophan and novatophan in the treatment of chronic gout. I agree with Dr. Stockton that uric acid is not by any means the whole story in gout, nor do clinical results always run parallel with the reduction of the uric acid content of the blood whether under the administration of atophan or the use of radium emanations. The most striking effect, clinically, of atophan in gout, rheumatoid arthritis and acute articular rheumatism is the relief of pain. In rheumatic fever the administration of atophan was always accompanied by relief of pain and fall in the temperature, but its withdrawal was followed by a recrudescence of pain and fever. It did not bring about recovery. For this, resort to salicylates was necessary. In cases of chronic gout, or in patients having a distinct gouty tendency, atophan given for one week in the month over a period of several months is helpful. Large doses are not needed, 1 gm. a day (divided into three 5-grain doses) is sufficient. It is not necessary to reduce the uric acid content of the blood to a theoretically normal standard. Gouty people have a higher normal uric acid index than others. It is only when this is exceeded that symptoms result. This is a natural consequence of evolutionary adaptation affecting every cell in the body. While 7 mg. or even 4 mg. per hundred cubic centimeters of blood is excessive for a normal man, it may not be equally excessive for one of gouty

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heredity. When the quantity of uric acid has been reduced to the equilibrium-point for the individual one should be satisfied; one does not hope to make the gouty cells of an entire body normal. With radium emanations I have had some experience and also with radium drinking-water but I have not sufficient data as yet for positive conclusions. In my dispensary service at Jefferson Hospital my assistants have made careful clinical observations which seem to show that better results can be obtained in the acute cases than in the chronic ones. It is possible that the remedy was not used long enough or strong enough. Our solution equals 50,000 Mache units per liter. The first effect of the radium treatment in cases of painful joints whether of gouty, rheumatic, or other origin, is to increase the pain, that is, providing one gets any effect at all. Unless one gets this exacerbation my observations have been that one cannot hope for a curative result. Apparently the agent acts on a sluggish local process, and reawakens the corrective reactions.

Dr. Arthur F. Chace, New York: In reply to Dr. Stockton, we have found that those patients having an intolerance for atophan can take it, well diluted with water, in small doses or in combination with soda. Novatophan has not proved as efficient as atophan. The determination of the uric acid content of the blood will aid in more accurately diagnosticating cases of gout. We do not call a case gout unless there is a concentration of uric acid of 4 mg. per hundred cubic centimeters of blood. It is interesting to note in other conditions the high uric acid content of the blood; for example, in uremia we have found a concentration of 14 mg. uric acid to 100 c.c. of blood. The amount of the uric acid content of the blood is an index of the severity of the case. In all clinical cases of gout in which there is a low uric acid concentration it is well to look for a possible focus of infection. With regard to the method of administration, it is wise to do as Dr. Cohen suggested, give the drug for one week in one month, or else alternate giving atophan for four days and allowing an interval of four days. In all cases the patients are placed on a purin-free diet. With purin-free and alcohol-free diet and without the use of drugs we have seen the uric acid content reduced from 6 to 3 mg. per hundred cubic centimeters of blood. With regard to the clinical influence of radium, we prefer to reserve our judgment until we have had an opportunity to extend our observations.

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INTRARECTAL ADMINISTRATION OF SODIUM SALICYLATE IN ACUTE RHEUMATIC FEVER WITH SATISFACTORY RESULTS

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In 1912, I published a report[1] covering 22 cases in which the intrarectal administration of sodium salicylate in acute rheumatic fever was apparently successful. The present report is based on 100 additional cases in hospital and private practice, the results of which indicate the advantage of this method over the usual modes of treatment in acute rheumatic fever and I would urge the adoption of the method at the hands of this representative body.

The intrarectal method of salicylate administration was adopted in 1911 on the East Medical Service in the Cincinnati General Hospital after observing the number of refractory cases of acute and subacute rheumatism in the wards. Previous to this, text-books had mentioned the possibility of such a method of treatment, while very meager reports had appeared in the literature (notably, however, Erlanger's in 1893 from the Klinik Von Ziemsen), but no attempt had been made to urge the general adoption of this measure as the method of choice. Erlanger[2] reported twenty-five cases with seventy-eight salicylate enemas and his report showed very satisfactory results with as small a dosage as from 6 to 8 gm. daily, and also gave satisfactory proof of the ready absorbability of the drug by the rectum.

1. Heyn, Louis G.: Acute Articular Rheumatism Treated by the Rectal Administration of Sodium Salicylate, The Journal A. M. A., April 6, 1912, p. 1013.
2. Erlanger: Deutsch. Arch. f. klin. Med., 1893, li-lii.

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But the value of the intrarectal sodium salicylate administration has not met any general recognition. Many other drugs have been given per rectum, most often for their local effect, as quassia, silver preparations, tannic acid, while certain others, as opium, digitalis, collargol, quinin and various serums have been used for their remote effects, but most of these latter if not to be administered by mouth may be used preferably by the subcutaneous method, a method not to be so readily adopted for salicylate medication, though Seibert reports satisfactory results. Heretofore we have permitted ourselves to be satisfied with the administration of sodium salicylate by mouth and the results have without doubt justified the designation of the drug as a specific in acute rheumatic fever.

The salicylic acid group of substances is bactericidal and according to Meyer and Gottlieb, salicylic acid is probably etiotropic, that is, acting on the cause of the disease. If the recent investigations of Pointon and Paine and Rosenow are to be regarded as conclusive, we must look to a bactericidal agent for rational therapy and in the absence of a specific serum or vaccine, sodium salicylate and certain newer salicylic acid preparations as, salol, aspirin, salipyrin remain our principal weapons in acute rheumatic fevers.

But why should there be so many failures with salicylic acid therapy, which is in every way to be regarded as a specific? No doubt in many instances there are foci of reinfection, in which surgical measures may be necessary. But in very many instances there has been insufficient dosage due most often perhaps to the frequent intolerance of the drug by mouth; and following on this failure the drug manufacturers have not been slow to introduce preparations more readily tolerated, but without doubt less efficient than sodium salicylate in the therapy of acute rheumatic fever. There is still much indifference among medical men toward pharmacology and therapeutics, perhaps inherited from the days of therapeutic nihilism, and if

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we fail in a therapy learned possibly in student days, many are apt to seek at once the new therapeutics as taught by the detail men.

If a routine administration of sodium salicylate has not always given brilliant results as it often does, however, the drug should not have yielded its position so largely to the newer salicylic acid preparations. As a solution to the problem of rheumatic therapy, intrarectal administration of sodium salicylates is offered as the method of choice and as excellent a therapeutist as the late Dr. Frederick Forchheimer declared it to be the best method yet devised for the treatment of acute rheumatic fever.

The method has for its justification its ability to answer the requirements of any therapeutic agent: (1) the ease of administration; (2) the ready absorption of the drug; (3) a minimum of untoward effects; (4) the ability to administer large quantities of the preparation as is to be advocated in bactericidal therapy; (5) the removal of the residue of the drug from the bowel by subsequent enema, if the dosage ever proves excessive; (6) the results are more prompt than by any other measure.

EASE OF ADMINISTRATION

I have used intrarectal salicylate therapy in 125 cases of joint affections, the majority of which occurred in hospital practice, where, to be sure, the method is most easily carried out. The method, however, lends itself readily to private practice as well. Recently in a severe protracted case of rheumatic fever occurring in a rural district, I advised the removal of the patient to a hospital in Cincinnati, in order to carry out the rectal therapy. The wife of the patient thought that she might be able to carry out the treatment at home and she did so and was promptly successful. I received a similar report from a physician in South Dakota recently and there is reason to believe that the method has been widely used since my report two years ago.

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The method of administration is as follows: A cleansing soapsuds enema is given and as soon as effective is followed by the salicylate enema given by means of a Davidson syringe and a rectal tube inserted 6 to 8 inches. The dose varies according to the size and sex of the patient and also according to the severity of the case. The first adult dose in men is usually from 8 to 10 gm., in women 6 gm., women being apparently more susceptible to salicylism than men. The synthetic salicylate has been used, especially since the clinical research carried out by the Council on Pharmacy and Chemistry, in which I had the privilege of assisting, the results of which proved the practical similarity in action of the synthetic and natural salicylates. The amount of salicylate to be given is incorporated in 120 to 180 c.c. of plain or starch water with the addition of 1 to 1.5 gm. of opium tincture. The dose of salicylate may be repeated in twelve hours, when it can usually be determined whether symptoms of salicylism will appear. Usually, however, a daily enema suffices with doses increasing perhaps from 30 to 50 per cent. daily until the limit of tolerance is reached. The largest daily dose which has been given has been 24 gm., and the only symptoms of salicylism which usually have appeared have been tinnitus and excessive perspiration. Once or twice there has been vomiting present, which might occur in the administration of even a simple enema. Where salicylism has been excessive, it usually appears within from three to six hours and the remaining unabsorbed portion of salicylate may be washed out of the bowel by subsequent enema. This has been resorted to very infrequently indeed, and it is rare also that the rectum is intolerant of the drug. I do not agree with Erlanger that the plain water enema is more readily retained than the starch water, although the former is more simple, which is in its favor. It might be said at this point also that salicylate medication must continue some days after all symptoms have subsided, otherwise recurrences are frequent.

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READY ABSORPTION

In testing out the value of this method it was interesting to note the promptness of absorption by the rectal mucous membrane. Usually within fifteen minutes, always within thirty minutes, a strong ferric chlorid reaction appeared in the urine and the reaction usually persisted for from forty-eight to seventy-two hours after the administration of the drug ceased.

To show also that complete absorption was usually possible, the stool subsequent to the salicylate enema was examined by acidifying with hydrochloric acid, extraction with ether and testing with ferric chlorid. As a rule usually within from twenty-four to thirty-six hours, depending on the size of the dose, there was complete absorption as shown by a negative reaction. (It would seem that the greatest absorption is within twelve hours.)

PROMPTNESS OF ACTION

Results show promptness of action. If we consider acute rheumatic fever as a disease which runs a most variable course, with a migrating involvement of usually many joints, each affected joint remaining at an acute stage of inflammation for several days, the attack possibly running a severe course of one or two months, often in spite of a more or less vigorous treatment (or there may be a less severe course involving fewer joints or perhaps only a subacute recurrent course of the disease) it may be readily seen that a satisfactory judgment of a therapeutic measure in this disease may be very difficult. A satisfactory therapeutic agent in acute rheumatic fever, however, should accomplish the following results: promptly lessen and eventually abolish all symptoms of the disease, materially shorten the course of the disease, reduce cardiac complications to a minimum and possibly prevent recurrences.

The following illustrative cases in which the intrarectal administration of sodium salicylate has been resorted to may be convincing.

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CASE 1.—Man, aged 32. Attack began ten days previous to admission to the Cincinnati Hospital, with successive involvement of the right hip and right knee, left knee and ankle and left shoulder. On admission the joints most acutely affected were the left elbow, left shoulder, left wrist and several phalangeal joints of both hands. The temperature reached 102 F. the first day. A salicylate enema of 10 gm. was given and a similar enema twelve hours later with complete cessation of symptoms and prompt drop of the temperature to normal. Three subsequent enemas of 10 gm. each were administered on three successive days with no recurrence or cardiac complications, the patient insisting on leaving the hospital four days after admission.

CASE 2.—Man, aged 34. On admission to the Cincinnati Hospital patient had a temperature of 103 F. and involvement of both knees and both ankles acutely. Ten gm. of sodium salicylate were given daily per rectum. The second day of residence in the hospital the temperature reached 102.4 F. and only the right knee remained acutely inflamed. The third day the temperature had reached normal and there were no joint symptoms remaining. The patient insisted on leaving the house on the fourth day.

CASE 3.—Colored woman, aged 27. Patient had involvement of both ankles and wrists and a temperature ranging from 101 to 102 during three days' residence in the hospital, during which time sodium salicylate (20 grains) was administered by mouth every three hours during the day. Symptoms were uninfluenced by medication per os. After a single salicylate enema of 10 gm. the temperature dropped to normal and remained there and there was a complete subsidence of symptoms. The enemas were continued for four days subsequently.

CASE 4.—Man, aged 39. Admitted July 16, 1912, with a temperature of 101.6 F., pulse 108. There was involvement of both knees and ankles and both shoulders and wrists. Sodium salicylate enemas of 10 gm. were given daily. Three days later there was a maximum temperature of 100 with maximum pulse 104 and all joints except wrists were improved. The fourth day 13.3 gm. of sodium salicylate were given with complete cessation of symptoms, but with some salicylism and the enemas were discontinued. On the fourth day after discontinuance of the enemas, however, there was some recurrence of joint symptoms and 13.3 gm. were administered for four successive days in spite of some tinnitus and excessive perspiration. The temperature became normal and the joint symptoms subsided completely within ten days, during which time a total of 100 gm. of sodium salicylate had been administered. This case was somewhat refractory on account of the salicylism, but we were able to carry the treatment carefully to a successful issue.

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These cases are fairly illustrative of the efficacy of the intrarectal salicylate therapy and if the more common methods of treatment in acute rheumatic fever have so often been disappointing, the intrarectal method is offered as a very safe and reliable solution to the therapy of this serious affection.

22 West Seventh Street.

ABSTRACT OF DISCUSSION

Dr. E. W. Mitchell, Cincinnati: I wish to corroborate the report made by my associate concerning the value of the rectal method of administering the salicylate. To obtain the specific action of the drug, the primary doses should be large. It is often quite difficult to give sufficiently large doses by the mouth. We have seldom found difficulty in giving by rectum from 75 to 150 grains, twice daily. That the drug is promptly absorbed is shown by its early appearance in the urine, as Dr. Heyn stated, and also by the relief of pain, reduction of temperature, etc. Notwithstanding these evidences of absorption, we have found almost constantly that the ringing in the ears, nausea and other unpleasant effects are much less marked than when given by the mouth. Why this should be so I do not know, unless the local irritation of the stomach is responsible for many of the unpleasant effects of the salicylate. We believe that salicylic acid is a specific, but that it must be given in large doses in the early stage of the disease. It has been objected that while salicylic acid itself is a germicide, its salts are very feebly so, and however given salicylic acid always circulates in the blood as a salicylate. Dr. Wood has recently offered an ingenious explanation in answer to this objection. His theory is that the excess of carbonic acid in the congested areas converts the salicylates into salicylic acid, enabling it to exert its germicidal or antiseptic power. I have also found the rectal method successful in private practice, whenever a competent nurse was in charge.

Dr. Joseph L. Miller, Chicago: Dr. Heyn shows that salicylates when administered by rectum are actually absorbed, but it is difficult to understand why salicylates by rectum in a certain dose should have a greater action than the same amount by way of the mouth, as, after all, it is apparently a question of the amount of the drug absorbed and we know that salicylates are readily absorbed by the gastro-intestinal tract. I believe one explanation of the excellent results Dr. Heyn obtained was the fact that the doses he employed were relatively large, larger in fact than the ordinary dose administered by mouth, and if the absorption was complete by the rectum it would have the same effect as if the

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equivalent amount were given by mouth. His work shows that in those cases in which the drug is not tolerated by mouth, it can be well taken by way of the rectum. I differ somewhat from Dr. Heyn, that salicylates are a specific in rheumatism, as statistics show that patients treated by salicylates remain in the hospital quite as long as those receiving other forms of treatment for their arthritis.

Dr. J. N. Upshur, Richmond, Va.: In the discussion of this subject a few years ago in this Section, a number of speakers stated that their practice was to give large doses of salicylates, often as much as 300 grains in twenty-four hours, that endocarditis was a troublesome sequel, and they were at a loss to explain why. I said then practically what I repeat now. In the treatment of rheumatism, a good dose of a mercurial should be given at the start. The pronounced acidity of the sweat and urine is a conspicuous symptom, indicating the administration of alkalies until these excretions are neutral. My practice is to give, well diluted in water, potassium bicarbonate, 10 grains every two hours for forty-eight hours, following it with small doses (5 grains) of sodium salicylate every two hours for about two days. Relief is usually prompt. I never give more than a dram of salicylate in twenty-four hours, and rarely that much. I believe that large doses of salicylates predispose to the development of endocarditis, and the patient is much more liable to relapse, than if a foundation is laid by the exhibition of the mercurial, followed by the alkali. I desire to enter my protest against these excessive doses of the salicylates as being most harmful and dangerous.

Dr. J. M. Rector, Columbus, Ohio: I have used this method successfully by a more satisfactory and thorough method. The solution is introduced into the colon with a large rectal tube to the point of toleration; the irrigator is then disconnected from the rectal tube and the solution forced into the upper parts of the colon by introducing air behind the solution with the aid of the Politzer bulb; the Politzer bulb is then removed and the solution which was not carried out of the sigmoid permitted to flow out of the tube. More solution is then introduced and the Politzer bulb again used until the entire colon is moderately distended. This traps the solution and carries it higher with a more equal distribution along the tract, increasing the surface through which the drug may be absorbed. This procedure is painless and I have been able to get better results with smaller doses in greater dilution, and this method also assists in elimination and drainage of the entire alimentary canal and leaves the upper part of the tract undisturbed so that it may follow its normal digestive activities uninterrupted. The three advantages are: 1. It increases the resistance of the patient by not disturbing the digestive ability in the upper part of the

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alimentary canal. 2. It increases the elimination and relieves all tendency to absorption from a constipated colon. 3. It gives the direct introduction of salicylate of soda in large doses with all its beneficial effects and without the digestive disturbances which usually follow the use of this drug by mouth.

Dr. James Tyson, Philadelphia: In 1896 my attention was called to the efficiency of this mode of administration of the salicylates advised with a view to getting rid of the unpleasant gastric symptoms so often associated with the use of salicylates by mouth. Of late years, however, it has been found possible to refine the salicylates so as to get their effects without the disagreeable nausea. Aspirin, for instance, is a result of such refinement, does not disturb the stomach nearly so much and is equally efficient, rendering administrations by the rectum less essential.

Dr. Nathan Rosewater, Cleveland: When salicylates first began to be used in the New York Hospital, in 1878, I saw enormous doses given with remarkably good results compared to the older methods. Germ life, metabolic and other causes have been studied since then. Knowing that salicylic acid is a powerful inhibitor of fermentation, 1 grain being sufficient to preserve a pint of fruit-juice or other saccharine fluid, it occurred to me years ago that in proportion to the body-fluid such doses were entirely out of proportion, and the unnecessary and perhaps harmful effects far in excess of that required to inhibit germ life. I began at first to give 10 grains in chronic lithemic cases, before meals, when the stomach was practically empty—at least then the salicylate would not inhibit the action of the proteolytic and carbohydrate enzymes—and in acute cases and later in all cases to give only 15 to 20 grains at bedtime, three or more hours after supper. During the day I depended first on alkaline laxatives, such as citrates and tartrates to empty the gastro-intestinal canal, and on sodium iodid and other haloid salts to reduce the viscosity of the blood-stream and to relieve the heart of overtension, sparing it and aiming to avoid damage to this readily damaged organ. By elevating the lower extremities and even the upper ones, using gravitation to assist the venous return and sparing the cardiac mechanism, my results have been most satisfactory. For instance, in a very stout woman, aged 67, with all the joints of the lower extremities red, swollen, and very painful, temperature 102 F. and the digital extremities also swollen, I succeeded in having her on her feet in twelve days, without relapse. I have not given atophan, although my colleagues have been instructed to use it whenever salicylates should fail. The same is true of other preparations which I have kept on hand but have had no use for, although I use and have prescribed annually for many years, with this

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small dosage, approximately 100 pounds of sodium salicylate, not the natural, but the ordinary synthetic quality. I am glad to see that Hanzlik at Lakeside Hospital has corroborated the fact that the so-called natural salicylic acid has no advantages over the U. S. P. synthetic product. I have never seen ill effects except rarely when the stomach was not empty, the hydrochloric acid still present, liberating sufficient salicylic acid to irritate the gastric mucosa into distress or even to cause vomiting.

Dr. W. W. Tompkins, Charleston, W. Va.: Our duty in this class of cases does not consist in how few days our patients are in the hospital, or confined in their homes, but our chief object should be that, when our patients get out, they should be free from endocarditis and its unpleasant symptoms. The question each physician should ask himself is how efficient is the patient after an attack of acute rheumatism? The method and dose of administration of a medicine is but secondary. Few of us have such large experience as Dr. Miller when he treats 2,000 cases by one method and 1,600 by another. Each of us has an experience, it may be relatively small; but what is important is the percentage of actual recoveries. When cases respond so readily to remedies as reported by Dr. Heyn may it not be that we would in such cases take a too optimistic view and not safeguard our patients for a few days or weeks by rest and freedom from work or exercise? Is it a safe practice to permit a patient four or five days after his initial symptoms to leave his bed or the hospital and go about or resume his vocation? If the joints of the lower limbs are involved we get a forced rest because it is painful and impractical to get about, but if a wrist or elbow is involved our patients can go about and will do so if we do not restrain them or admonish them as to their danger. The reduction of fever and the allaying of pain should be aimed at, but the important point to keep in mind is the specter of a diseased heart with all its unpleasant sequels. Dr. Heyn mentions treating 124 cases by this method—quite a large number. Will he please state how much lower his percentage of endocarditis is than we have by the method of administering the salicylates by the mouth. It is to the hospital clinician that we look for our statistics in these matters.

Dr. Louis G. Heyn, Cincinnati: I desired to state in the paper the results, in general, of the therapy and to cite a few instances fairly illustrative of the response of a class of cases to a definite line of therapy. The proof of the methods suggested must rest on the observations of those who are quite impartial in their judgment of results obtained. Dr. Miller's discussion was enlightening to me. It may be that what he said is a strong argument against the bactericidal effect of the salicylates, for he injected various

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bacteria and then gave the salicylates with apparently no effect on the bacteria, which would tend to prove that the salicylates have no bactericidal effect. Salicylates have apparently never had any effect where there is evidence of a general bacteriemia as would be indicated by an endocarditis, and animal experimentation and clinical results are not always in accordance. The more I see of cases of acute rheumatic fever and the promptness with which this affection reacts to the salicylates the more I am inclined to believe that the drug must have some direct effect on the bacteria in this affection. I am quite in accord with the alkaline therapy with its frequently good results; it is also well known that many patients recover without any therapy, but there are few diseases causing such severe suffering as acute rheumatism, and most of us will at least seek the analgesic action of the salicylates. I must again answer the contention for the drug by mouth. Large doses by the mouth are possible and effectual in many cases, say from 20 to 30 grains five times a day, but this amount cannot be continued many days. The attack may be subdued within ten or twelve days; but not always, as Dr. Rosewater contends. On the other hand, one sees many cases prolonged weeks or months even in spite of the salicylate treatment. Someone has said that the salicylates predispose to cardiac affections. I have given it even in cases of marked cardiac arhythmia and have seen no untoward effects, so far as I could judge. Dr. Rector's suggestion that this method of administering the enema be modified by the use of the Politzer bag, instead of the Davidson syringe in our method, would seem feasible. As to Dr. Tyson's statement that there is no further need of the use of sodium salicylate since the introduction of the newer preparation, notably aspirin, I am not prepared to endorse his views, although this may be so. I am surprised to learn that Dr. Tyson had used intrarectal salicylate so many years ago, and had I known it I should have incorporated the fact in this paper. Relative to the number of cases of endocarditis following this method of treatment, I have seen only one case in which endocarditis developed during the attack. Occasionally an apparently cured patient with rheumatic fever has been discharged from the hospital and at the next observation some time later, we have found a valvular lesion. It is difficult to determine whether it is subsequent to the previous rheumatic attack or due to a mild infection in the interval between the rheumatism and the appearance of the valvular lesion.

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NEWER POINTS OF VIEW REGARDING THE PART PLAYED BY DIFFERENT FOOD SUBSTANCES IN NUTRITION

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For the continued performance of their physiologic functions and for the maintenance of their material integrity, living organisms are dependent on an adequate supply of suitable nutrients. Their needs in this respect are evidently not uniform at all times. Periods of growth and development, of convalescence and repair, determine special requirements that are not encountered at other epochs in the life-cycle, just as rest and activity alternate in making unlike demands on the organism during the routine of each day. It was realized, long ago, that these varied manifestations of the bodily mechanism may create specific demands in respect to the food substances; but it was a forlorn hope to expect to penetrate far into the mysteries of nutrition until some definite and fairly comprehensive knowledge regarding the chemical make-up of the products taken into the body as food had been unveiled. An elementary understanding of the fate of the fats and carbohydrates came earliest, because these foodstuffs were the first to have their chemical constitution unraveled. The story of the metabolism of the protein substances is only now beginning to keep pace with the newer knowledge of the structure of these highly complex nitrogenous compounds, and there are chapters bearing on numerous other factors in the food intake — on the place of the inorganic

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salts, the lipoids and diverse accessory features in the dietary — that still remain to be written even in their broadest outlines.

To speak of "newer" points of view regarding the rôle of the different food substances in nutrition, as I am expected to do, implies a contrast of to-day with yesterday in this progressive domain of physiology. One need not turn back far to reach the days of Liebig, to whom, above all others, are due the beginnings of present-day knowledge of the constitution of foods, tissues and excreta. In Moleschott's popular "Physiologie der Nahrungsmittel," published in 1859, the chief concern of nutrition was portrayed as the production of good blood. He wrote:

> One of the foremost questions which humanity will always address to the physician, is how good, healthy blood, capable of development, can be attained. And, modify the inquiry as they will, all those who are concerned therewith are forced by experience to admit, whether it be frankly or with reserve, that our thoughts and our loves, our children and our powers depend on our blood—and our blood on food.

Accordingly, Moleschott further maintained that vigorous nutrition is the consequence of efficient formation of blood; so far as the latter process means an enrichment of the circulating fluid in protein substances, the vigorous nutrition would express itself, above all, in the muscular tissues. "The more meats, legumes and cereals are consumed and digested," says Moleschott, "the plumper are the muscles, the firmer their fibers, the more powerful their action." Other diets, of rice, or vegetables, or fish, were pictured as leading to an enfeebled musculature. For the fats and carbohydrates there were known depots other than the muscles. Not until the work of Carl Voit was the principle of nitrogenous equilibrium definitely established for the animal body.

The vague and indefinite generalizations of a generation ago in respect to the functions of the foodstuffs have slowly been transformed into the more

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tangible theories and suggestive hypotheses of the passing decade. To give you some more concrete ideas of what these changes have involved I may refer to the teaching current in my own student days, more particularly as it is related to nitrogenous metabolism. Sir Michael Foster wrote in 1891: "At all events the greater part of the proteid material of the food enters the blood as proteid material, either as peptone or in some other form, and is carried as proteid material to the tissues." The latest dictum respecting this phase of absorption presents an entirely different point of view. Proteins are now understood to be disintegrated in the digestive tract into relatively simple nitrogenous fragments, the amino-acids, not exceeding twenty in number. It is these digestion products, absorbed into the blood-stream and now demonstrated beyond peradventure to be present there, that represent the real form in which the protein intake of the body is transported throughout the organism. Protein metabolism has at length become essentially a question of the behavior of amino-acids in the body — their uses and fate.

So far as the nitrogenous transformations are concerned, the amino-acids are the center of interest in nutrition, the pivot about which the modern conceptions turn. For him who would understand the real significance of the proteins in the functions of the organism there is no escape from the necessity of appreciating clearly the nature of the amino-acids — those derivatives which arise when, either in the laboratory of the chemist or in the alimentary processes of digestion, albuminous substances are disintegrated. A generation ago it was the superficial distinctions between animal and vegetable proteins, between albumins and globulins and albuminoids that formed the basis for discussions of relative nutritive merit. To-day we are more concerned with the question whether this or that protein, whatever its biologic

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origin, will yield the characteristic, desired amino-acids, such as tyrosin and tryptophan, leucin and lysin, glycocoll and cystin, histidin and arginin. Our attention is fixed on the building-stones or units out of which the great protein structures are put together.

Instead of referring to the proteins in terms of their physical properties or empirical composition — their content of carbon, hydrogen, oxygen, nitrogen or sulphur — at least so far as the problems of nutrition are involved, the time has arrived for estimating their behavior in the organism on the basis of the quota of each of about eighteen well-defined amino-acids which the individual representatives of this group of food-stuffs can yield. Most, if not all, of these amino-acids are essential for the construction of tissue and the regeneration of cellular losses. In proportion as any specific protein can furnish these constructive units it may satisfy the nutritive needs of the body. The efficiency of the individual protein in this respect must depend on the minimum of any indispensable amino-acid that it will yield; for it is now known that some of them cannot be synthesized anew by the animal organism. If, for example, a protein or mixture of proteins comparatively deficient in their yield of the sulphur-containing amino-acid cystin be furnished alone to supply the body's nitrogenous requirement, the production of new, cystin-yielding molecules of protein will be limited by the amount which is available in the diet. An excess need not be wasted, for it can be burned up like sugar or fat to provide energy; but new construction or growth is limited by the minimum of the essential unit.

Although a supply of all or most of the characteristic amino-acids derived from typical proteins is essential for the construction of new tissue or the repair of the old, it by no means follows that all of them are inevitably needed in the ordinary function of maintenance, that aspect of nutrition characterized by the preservation of unchanged body-weight in the

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adult from day to day. Nevertheless, certain amino-acids are absolutely indispensable even in maintenance. This is well shown in recent observations conducted by Osborne and myself under the auspices of the Carnegie Institution of Washington. We have succeeded in keeping small animals (albino rats) during long periods on mixtures of isolated protein, fats, carbohydrates and inorganic salts as they are present in the protein-free fractions of milk. The advantage of this experimental procedure lies in the fact that it is possible to test, as we have done, the nutrient efficacy of individual proteins. The upshot of our now extensive experience has been to demonstrate pronounced differences in proteins from different sources. Some, like the proteins of milk, the edestin of hemp-seed, the albumin of egg-white, are individually capable of satisfying the nitrogenous needs of the body at all stages of its development. Chemical analysis has disclosed the potential existence of most of the familiar amino-acid groups in each of these protein complexes. When the gliadin of wheat, a prominent protein of this seed, is fed as the sole protein, adult animals are suitably maintained; but growing animals cease to increase in body-weight, remaining in nutritive equilibrium without growth, unless the amino-acid lysin $\begin{array}{l}CH_2.CH_2.CH_2.CH_2.CH.COOH\\ \quad\;\; | \qquad\qquad\qquad\quad\;\; |\\ \quad\;\; NH_2 \qquad\qquad\qquad\quad NH_2\end{array}$ is added to the gliadin-food. Thereupon growth is promptly resumed. The explanation becomes apparent in the fact that gliadin is almost entirely devoid of the lysin radical; and inasmuch as this is obviously needed for new protein construction, growth cannot proceed until the missing unit is supplied. Again, zein, the most conspicuous protein of the maize kernel, fails to yield either lysin or tryptophan $\begin{array}{ccc} & C\text{—}CH_2.CH.COOH & \\ \diagup & \quad\;\; | & \\ C_6H_4 & \quad\;\; CH & NH_2 \\ \diagdown & \quad\;\; | & \\ & NH & \end{array}$ or glycocoll $\begin{array}{l}CH_2.COOH\\ \quad\;\; |\\ \quad\;\; NH_2\end{array}$ and accordingly is entirely inadequate to meet the nitrogenous needs of animals in respect to either main-

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tenance or growth. It may be fed in the greatest abundance; yet the animals decline in health unless the zein is supplemented by some more perfect protein. If the amino-acid tryptophan is added to the imperfect maize protein, maintenance of body-weight, without growth, is promptly established. Evidently tryptophan is indispensable for some physiologic function quite apart from increase in tissue substance. If both tryptophan and lysin are added to the zein, the diet thereupon becomes suitable for growth. In glycocoll, likewise missing in zein as in several other proteins, we have an instance of an amino-acid which can undoubtedly be manufactured when it is needed. From these facts it is apparent how essential certain amino-acids are in the nutritive processes and how unable the body is to synthesize some of these anew.

I trust that this hasty review has given emphasis to the contention that the problem of protein metabolism has largely become one of amino-acid supply. Provided only that they are rendered free and available by the digestive processes, the body cares little whence its amino-acids are obtained. Meat proteins, egg proteins, cereal proteins—all serve in the same sense. Indeed, the amino-acids themselves, isolated in the chemical laboratory, appear to be equally available. We begin to understand why a diet largely made up of corn with its abundance of the imperfect zein and its relative poverty in more complete proteins may be poorly suited for growing individuals; why corn is so advantageously supplemented by a little skimmed milk with its casein and lactalbumin; why gelatin, which does not yield tyrosin, tryptophan or cystin, fails by itself to meet the demands of the body for nitrogenous pabulum; why a low intake of a suitable protein may be infinitely more advantageous to nutrition than a surfeit of an "incomplete" protein.

Nor is the story of the rise of the physiology of the amino-acids ended here. These compounds furnish a superior medium for the growth of bacteria, not infre-

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quently yielding products of pronounced toxicity or pharmacologic potency. A series of amins ranging from simple forms to complex types owe their origin to the action of micro-organisms on proteins, both outside of the body and within the alimentary tract. Putrescin, cadaverin, tyramin, histamin are derived from the amino-acids arginin, lysin, tyrosin and histidin, respectively. Likewise the widely vaunted alimentary offenders, indol and skatol, are chargeable to the putrefaction of the tryptophan group in the protein molecule; phenol and cresol are similarly derived from tyrosin. Thus many of that vague and heterogeneous collection of compounds once convincingly included in the indefinite expression "ptomains" are doubtless nothing else than the fragments of amino-acids that have fallen sacrifice to bacteria before they could be absorbed intact into the blood-stream. Now that the production of these more or less toxic amins and alcohols is clearly referable to the action of known types of bacteria on individual amino-acids, the way to avert the malaise or more serious consequences with which the putrefaction products are so often charged may be a step nearer. Gelatin, for example, furnishes no tryptophan, tyrosin or cystin; the intestinal bacteria are therefore unable to liberate indol, phenol, hydrogen sulphid or mercaptans from it.

To still another domain the discovery of the amino-acid structure of the proteins has admitted fresh rays of light. The phenomena of immunity, creating almost an entire new science of immunology; the precipitin reactions; anaphylaxis and its varied manifestations—all of these point to the participation of proteins; and, what is more significant, owing to the highly specific character of the responses, they postulate the existence of individual proteins in numbers far exceeding the possibilities suggested by the ordinary criteria of individuality. How are we to conceive of a hundred

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or a thousand specific albumins from as many tissues and individuals? We need merely grasp the convenient hypothesis furnished by our knowledge of the amino-acids which they yield. Assuming that ten different amino-acid derivatives are united even without duplication to form a single protein, mathematical calculation indicates the possibility of over three million different combinations; for eighteen amino-acids the possible combinations have been estimated to exceed millions of millions. In the face of such figures one realizes what specificity may really mean when thousands of structurally isomeric compounds can theoretically, at least, yield precisely the same proportions of the same amino-acids and yet remain distinct in respect to the relative arrangement of their constituent units. The development of an almost innumerable number of special enzymes, as suggested by Abderhalden's recent studies now widely applied in serodiagnosis, likewise finds the possibility of an explanation in what has just been noted. A thousand structures may require a thousand different keys to unlock them.

It might be illuminating to dwell further on other consequences entailed by the development of the biochemistry of the amino-acids; but we must return again to the physiology of two decades ago for a reminder of other changes that have been wrought by the hands of progress. Urea was, of course, recognized as the predominant excretory end-product of nitrogenous metabolism. Its history was difficult to follow, and almost entirely obscured. Foster voiced a then current belief in his widely studied text-book in suggesting that a large portion of the urea leaving the body by the urine is formed from the creatin of the muscle, though the objections to such a theory were already obvious to him. The normal presence of creatinin in the urine offered a difficulty which was not entirely solved by charging its origin to creatin

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ingested as meat. Nor was only creatinin left as a source of confusion. Uric acid and other excreted products remained to be accounted for, as they occurred in varying amounts in the urine.

Foster wrote:

> Urea is the chief end-product of proteid metabolism, but that end is probably reached in several ways; so that probably a very large number of nitrogenous chemical substances make a momentary appearance in the body. Some of these fail to become urea, and either without or after further change make their appearance in the urine. But we do not know whether their appearance is accidental, the result of imperfect chemical machinery; or whether they, though small in quantity, serve some special ends in the economy. Perhaps sometimes, or with some of them it is the one case, at other times or with others it is the other case. . . . The evidence as far as it goes tends to show that the metabolism of proteid is very complex and varied, that a large number of nitrogen-holding substances make a momentary appearance in the body, taking origin at this or that step in the downward stairs of catabolic metabolism and changing into something else at the next step, and that the presence in various parts of the body and even in the urine, in small quantities, of so many varied nitrogenous crystalline substances, forming a large part of what are known as extractives, has to do with this varied metabolism. Possibly the transformations by which nitrogen thus passes downward take place to a certain extent in such organs as the liver and the spleen, which are remarkably rich in these extractives. But the whole story of proteid metabolism consists at present mostly of guesses and of gaps.

In this veil of mystery that surrounds the chemical transformations of the food-substances in the body there are today many rifts through which new truths have been brought to light. Uric acid is no longer associated with the metabolism of the simple proteins, but is recognized as the excretory end-product of the purins, a group of compounds distributed widely in nature, either free or combined as they are in the nucleoproteins of cellular tissues. By the exclusion of glandular material, like liver and sweetbreads, and of meat with its free hypoxanthin, the dietitian can reduce the production and output of uric acid in man at will. Here is one of the striking instances of where, through the newer knowledge of foods and metabo-

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lism, the physician has become a master of the chemical performances of the organism. The creatinin of the urine, provided that it is not reinforced by ingested precursors in meat, represents a story of the inner workings of the organism quite independent of the protein in the diet. The ammonia output is in a measure an index of the overproduction of acids in the body. Although by no means the only regulatory device whereby the neutrality of the blood and tissues is maintained in health, ammonia is nevertheless automatically furnished in conspicuous amounts when it becomes necessary to offset an impending acidosis. Hitherto the therapeutic procedure in such cases has been to furnish an alkali, commonly sodium bicarbonate, and thereby conserve the available supply of bases in the body from depletion. Recent studies have shown that a similar contribution of bases is afforded by a judicious selection of the dietary. There are foods which act as potential acids and others which function as bases in the organism. When burned up either in the laboratory or in the body-cells, they leave a preponderance of acid or base, as the case may be, in their ash. In this respect potatoes, apples, raisins, and cantaloupe, for example, are base-forming foods which depress the output of ammonia and increase the solubility of uric acid in the urine, as the experiments of Dr. Blatherwick in our laboratory have demonstrated; whereas meats, cereals and prunes (the latter with their content of benzoic acid) furnish acids in preponderance. Milk is intermediate in this respect. From the point of view here raised it is quite easy to accomplish as much with a liberal allowance of certain selected foods as with half an ounce of the familiar bicarbonate. To do this, however, implies that the physician must become as well acquainted with the properties of the foods as he appears to be with such novelties as amboceptors and complement, polyvalent vaccines and immune serums, salvarsan and epinephrin.

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Turning attention to another group, the fats, the question must have arisen in the minds of many a physician as to why certain representatives of these foodstuffs have so long maintained a reputation for superior merit in connection with nutrition. There are several fluid fats which are quite as available, or even more easily procurable than is cod-liver oil. Yet this product continues to enjoy a vogue that cannot be dismissed as the mere result of advertising propaganda. Cod-liver oil was a favorite, particularly in the dietotherapy of children, long before the present era of catch-phrase circulars and illuminated billboards. Its supposed unique virtues have called forth varied attempts at explanation. At one time it was the trace of iodin found in cod-liver oil which was believed to endow it with superiority over other fats like cottonseed oil and olive-oil having essentially the same physical properties and the same mixtures of glycerids, or fats proper. When this explanation no longer appeared tenable, the superior value of cod-liver oil was attributed to its ready digestibility. Lately Osborne and I have observed an unexpected efficiency in the product which is not shared by many other fats of similar superficial properties. We have fed growing animals (albino rats) on mixtures of isolated food substances including an abundance of fat in the form of commercial lard until, owing to the lack of some essential and as yet unknown ingredient of adequate dietaries, growth was checked. The replacement of a portion of the lard in the diet by cod-liver oil invariably brings prompt restoration of growth which continues uninterrupted until the adult stage is reached. Butter-fat and egg-yolk fat likewise contain a "growth-promoting"ingredient which appears to be more or less completely wanting in other dietary fats of both animal and vegetable origin. There is, for example, a marked difference between lard and the fat elaborated by the mammary gland. Whereas our experimental animals show symptoms of malnutrition with a cessa-

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tion of growth and decline in weight at the end of three months on a diet including lard as the sole fatty ingredient, when either butter-fat or cod-liver oil were used there was no sign whatever of failure after a year or more of uninterrupted feeding on the same diet day after day.

It is well known that all of the naturally occurring fats, such as have just been mentioned, are complex mixtures of true fats in the chemical sense, along with other substances including lipoids, pigments and compounds more soluble in fat than in the watery mediums of the body. The lipoids, in particular—cholesterol, lecithins, cephalins — have come into prominence in connection with various reactions involved in serum diagnosis and such phenomena as hemolysis, narcosis and absorption. Though long recognized as a constituent of the nervous tissues and certain pathologic products such as gall-stones, cholesterol has remained a compound of unknown function until very recent times. At the present moment the consensus of opinion appears to be that cholesterol is not ordinarily formed within the organism of the higher animals, and that these are dependent on the food intake to maintain the essential supply thereof. If this be true the ultimate source must reside in constructive plants; and assuming occasional losses from the body, doubtless with the feces, the store of cholesterol can be kept intact in man only by renewal from a suitable dietary. Ordinarily, in the adult living on a ration of products derived from many sources, no difficulty arises, because compounds of the cholesterol type are widely distributed and presumably found in all cells; but it is quite conceivable that in individuals like growing children or patients living on a diet restricted in character a real deficiency of cholesterol may ensue. It is known that the hemolytic phenomena of the red blood-cells are related to their lipoid content; and the therapy of the future may find a place for such substances as cholesterol, kephalin, etc., in the management of hemolytic

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anemias and other pathologic manifestations. Here, again, the intricacies of the diet cannot be overlooked by the intelligent physician of the future.

I have dwelt somewhat on the possibilities in respect to cholesterol and the growth-promoting components of milk-fat, egg-fat and cod-liver fat because it affords an opportunity to emphasize the hitherto largely unappreciated importance of factors in nutrition which cannot be expressed in terms of the familiar protein, fat and carbohydrate or in calories of energy. These factors may be inorganic in some cases, as is instanced by the reputed rôle of iodin and the wide distribution and alleged significance of manganese, boron, silicon and other elements in animal tissues; they are frequently organic in character. To class these varied factors together under the euphonius designation of "vitamins," as has lately been done, does not render less obscure the deficiencies which the absence of them from the diet may entail; nor does it give any clue to the mechanism whereby growth may be promoted, metabolism stimulated, or deficiency diseases engendered. Not only in those admitted instances of diet deficiencies such as beriberi and scorbutus, but also in numerous other clinical and experimental types of malnutrition there is need for further research. The proverbial adherence of the medical profession to dogmatic statement must be changed. Its members must become eager to take up the current views, study the underlying data as well as they can, and watch the consequences. Let us welcome the day when the food market and the kitchen are taken into consideration by the physician as seriously as are the apothecary's shop and the fashionable spas.

If in all the foregoing little mention has been made of the carbohydrates in nutrition, it has been because, in a general way, more has been known about them for a longer time than is true of the other nutrients. Even among the carbohydrates the principle of speci-

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ficity comes into play. The physiologic carbohydrates are the six-carbon sugars, such as glucose, levulose and galactose. Unless an ingested carbohydrate can be converted into this simple type of sugar in the alimentary tract, its nutritive value is distinctly impaired or entirely lost. For this reason, all attempts to introduce more complex sugars, dextrins or starches directly into the blood-stream, for prompt distribution to the tissues which need them, have failed. In experiments conducted in our laboratory, animals have received subcutaneous or intraperitoneal injections of cane-sugar or milk-sugar for weeks and months without acquiring the capacity to utilize so little as a single gram introduced in this way in an undigested form. Carbohydrates like inulin and the galactan of agar-agar or of Irish moss can furnish no energy to the human organism because it is unable to digest them, that is, to convert them into simple sugars. The possibility of nourishing an individual in some way other than by the oral path evidently depends on introducing the nutrients in the form of those units—the amino-acids, simple sugars and fats—which normally constitute the actual pabulum of the hungry cells.

Physiology has borrowed its methods largely from the sciences of physics and chemistry. It also has a fruitful method of its own, that of experiments on animals and man. None of these procedures can be dispensed with. They corroborate and supplement each other, and they serve to test the hypotheses which give the impetus to progress. The medical profession must insist on conserving for the physiologic sciences the opportunity to continue its studies untrammeled by the passing prejudices of those who fail to appreciate its motives.

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INTERMEDIARY PROTEIN METABOLISM

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The subdivision of protein metabolism into intermediary metabolism and tissue metabolism indicates that we to-day are in possession of a much more detailed and accurate knowledge concerning animal metabolism than was available a few years ago. The controversy between Voit and Pflüger and their followers of the past generation as to whether the protein of the food must be incorporated in the protoplasm of the tissues before it is oxidized was an unprofitable and useless controversy, because it was too far in advance of the experimental knowledge of that period. We still do not know the spatial relationship between protoplasm and food materials at the moment of oxidation. On the other hand, we no longer speak of protein metabolism as being an oxidation process at all in the sense understood by Pflüger and Voit. While protein materials like other carbonaceous food materials are of course finally oxidized in the body, we now believe that the nitrogenous foodstuffs first undergo changes and chemical transformations involving the loss of all protein characteristics before they are completely destroyed by the oxidation processes involved in the production of heat and energy. Through the investigations of Kutscher (1898), and more recently of Abderhalden and his associates, it has been made clear that protein materials are completely decomposed into simple crystallizable products, the amino-acids, as a result of digestion. This discovery is fundamentally important for it has necessitated a complete revision of the earlier ideas and

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doctrines as to the nature of the metabolic processes involved in the utilization of protein as food. The old, burning question as to whether protein must be incorporated in the living tissue protoplasm before it is oxidized we now know was a false question, because the food protein has been altered beyond recognition even before it leaves the digestive tract and many of us no longer believe that protein as such is ever oxidized in the body.

The discovery that protein materials are split up into the simplest possible component parts during the digestion suggested two new fields for metabolism investigations. The first of these is the question as to whether simple amino-acids can be substituted for ordinary food protein, and which if any of the amino-acids are most indispensable for the maintenance of the animal organism. Much interest and important work has been done in this field, and it has become quite clear that some amino-acids are indispensable while others appear to be less necessary constituents of the food. The importance of all these data to the science of metabolism, if not to medicine, is self-evident in view of the fact that practically all the amino-acids can be manufactured. The second metabolism problem which required renewed investigations when the deep-seated character of protein digestion became clear concerns the subsequent history of the digestion products, and inasmuch as my own investigations lie in this field, I shall confine myself to a discussion of this problem.

Formerly it was generally believed that protein materials were but little altered by the digestion, and the protein of the food was supposed to pass into the blood-stream without any material alteration. Since no peptones were found in the blood the peptones formed during the digestion were supposed to be regenerated into more complex albuminous materials while passing through the mucous membrane of the intestinal wall just as fatty acids and glycerin are

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believed to be transformed into neutral fats during the absorption. This hypothesis seemed plausible, because it agreed with the experimental observations and because the animal organism was supposed to be dependent on the complex kind of proteins found in the blood. Many investigators, including Kutscher and Abderhalden, adhered to this explanation of what happens to the nitrogenous food in the intestinal wall even after it became certain that amino-acids and not peptones were the chief end-products of the digestion. Many physiologists, however, abandoned the protein regeneration hypothesis about ten years ago. To them it seemed highly improbable that the proteins should first be completely split up into amino-acids only to be immediately recombined into albumin and then again immediately broken down so as to give the urea, the elimination of which is greatly increased three or four hours after the intake of protein food.

In place of the protein regeneration hypothesis these dissenting physiologists assumed that the transformations of nitrogenous materials which take place in the intestinal wall are of a destructive rather than of a constructive character. Just as the digestive ferments convert the proteins into amino-acids within the digestive tract, so by a continuation of the digestive or hydrolytic processes most of the amino-acids immediately lose their nitrogen while passing through the intestinal wall and the liver. The prompt formation of urea, the supposedly large amount of ammonia in the portal blood, and many other features of the nitrogen metabolism were explained in a fairly plausible fashion by this hypothesis.

There remained, however, another possibility, namely, that the intestinal wall does nothing to the amino-acids but simply lets them through. From a theoretical aspect, this point of view has been the most plausible, and notwithstanding numerous early failures, the efforts to prove that the amino-acids are absorbed from the intestine without change have been

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continued, and now there is no longer any doubt about the fact that the end-products of protein digestion, the amino-acids, are quickly and easily absorbed. In fact, the speed of the absorption and the speed with which the amino-acids are distributed to all the different tissues in the body is one of the reasons why the earlier investigators failed to find the digestion products in the blood.

By means of the quantitative colorimetric methods devised in my laboratory, by means of Van Slyke's micro method, and by means of Abderhalden's qualitative ninhydrin test it is now easy to show that the amino-acids are absorbed. We have therefore now not the slightest reason for believing that the amino-acids formed during the digestion undergo any change while passing through the walls of the intestine.

The essentials of the story of protein digestion and absorption appear to be very clear indeed, and can be stated in two or three sentences. In the stomach the greater part of the protein is dissolved and much of it is converted into albumoses and peptones. In the intestine the dissolved products as well as the remaining undissolved residues are attacked by the trypsin and are thereby split up into amino-acids. The intestinal wall yields another ferment, erepsin, which, so to speak, prevents the absorption of albumoses and peptones by converting such as may escape the action of the trypsin into amino-acids — and the amino-acids as fast as they are formed are absorbed and transported by the blood to all parts of the body.

The absorption of amino-acids from the blood by the different tissues and organs is extraordinarily rapid, but is not complete. The communication between the blood and the tissues appears to be about equally good in either direction, and the accumulations of the nitrogenous digestion products in the blood and in the tissues reach therefore substantially the same level. This is, I think, true for the nitrogenous waste-products as well as for the digestion products, and if

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correct is important, for it means that by analyses of the blood we determine also the concentration or accumulation of the same products in the tissues.

The speed of the absorption is not the same for all tissues. The liver, for example, according to Van Slyke, absorbs amino-acids from the blood more rapidly than do the muscles even when the amino-acids are injected into the general circulation, and similar though smaller variations will doubtless be found in the speed of absorption revealed by different muscles; but such variations are probably only temporary, so that on the whole it will be found true, I think, that the concentration of a given nitrogenous product in the blood is the same as in such general tissues as the muscles.

In view of the established fact that the muscles absorb the greater part of the amino-acids coming from the digestive tract, it is no longer permissible to regard the liver as the chief seat of the urea formation. The greater part of the urea formation represents nothing but the removal of the nitrogen from amino-acids which are not needed for the rebuilding of new tissue material, and there is in my judgment no reason to doubt that the muscles which absorb the greater part of the amino-acids also form from them the greater part of the urea. Dr. Denis and myself have repeatedly emphasized this point of view, and recent studies made in the Harvard Medical School by Drs. Fiske and Sumner on the urea formation have clearly indicated that this process is not localized in the liver.

In its broad outlines the intermediary protein metabolism appears now comparatively simple and clear. The blood gets amino-acids from the digestive tract and all the tissues get them from the blood. From the amino-acid mixtures thus received each tissue rebuilds itself, and the amino-acids which are not needed for such synthesis are converted into urea and carbonaceous remainders. The latter are either con-

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verted into carbohydrates or are otherwise oxidized for the production of heat and energy. When protein materials from within the body are broken down, as in fasting and in fevers, these are in all probability digested in the tissues down to the stage of amino-acids, and from that stage on undergo the same transformations as do the amino-acids derived from the food.

According to this view it is to be noted that the specialization of functions which characterizes the higher animals does not extend very far into the field of general protein metabolism. All the tissues probably take part in this process roughly in proportion to the weight of living protoplasm contained in them. We cannot therefore expect to find the general protein metabolism materially or specifically altered because of this or that disease in any particular organ. I feel it incumbent on me to emphasize this aspect of the case, for we laboratory workers are often expected to elucidate diseases by metabolism studies when no such elucidation is possible on the basis of the available fund of knowledge of metabolism processes.

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THE SPECIFIC DYNAMIC ACTION OF THE FOODSTUFFS *

GRAHAM LUSK
NEW YORK

The conclusions to be reported in this paper are based on results obtained from 250 experiments on dogs. The animals rested quietly in a respiration calorimeter, at an environmental temperature of 26 C. (78.8 F.), and were subjected to different dietary conditions. Under these circumstances the simplest nutritional elements can be given and their effect on the heat production can be noted in hourly periods. This gives an idea of the interplay between the nutrient particles and the oxidizing tissues.

Dr. Du Bois will present the story from the point of view of investigations made with a similar though larger respiration calorimeter devised to determine the nutritional condition of the human being in disease.

All nutrient proteins, starches and compound sugars undergo fragmentation in the intestinal tract into simple chemical substances which are soluble in the fluids of the body. A polysaccharid like starch is broken up into glucose molecules; a disaccharid like cane-sugar (sucrose) is split into a molecule each of glucose and fructose, and lactose undergoes similar transformation into a molecule of glucose and one of galactose. Glucose, fructose and galactose are sugars which may be absorbed and carried to the living cells by the blood-current that bathes them. In similar fashion, the protein molecule is demolished in the intestine and broken into units such as glycocoll

* From the Physiological Laboratory of the Cornell University Medical College, New York.

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(amino-acetic acid), alanin (aminopropionic acid), glutamic acid, which is a dibasic amino-acid with five carbon atoms, and there are many others. These amino-acids are absorbed into the blood-stream and are carried to all the living cells of the body.

The result of the ingestion of food in any quantity is to increase the amount of heat production in the body. The extent to which the increase in metabolism occurs depends not only on the quantity, but also on the kind of food introduced into the blood-stream. Since the power to increase heat production exerted by protein, carbohydrate and fat is different for each substance, Rubner has defined this power as the specific dynamic action of the substance. The term is technical and cumbersome, yet the meaning is perfectly simple.

Every one has experienced the increased feeling of warmth after a hearty meal, and no one eats largely of meat in midsummer, for it increases heat production and consequently increases sweating.

The reason why the various foodstuffs increase heat production has not been entirely clear and it is this somewhat complicated problem with which the present paper deals.

In the first place, the increase in the heat production has nothing whatever to do with the increase in intestinal activity (*Darmarbeit*), a theory advocated by Zuntz; for the heat production is not increased by the ingestion of insoluble substances like bones or agar-agar, of saline cathartics even with the production of violent intestinal movements, or of Liebig's extract, which stimulates the glands to secretion. Likewise, incombustible substances such as urea and sodium chlorid when given in health, and glucose when given in diabetes, may be absorbed, carried in the blood-stream and eliminated in the urine without causing an increase in the oxidative processes. These facts have been established by Rubner, by Benedict and by others.

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When, therefore, the heat production of a dog rises 30 or 40 per cent. after glucose has been given, and even 90 per cent. after a large quantity of meat, it is evident that the cause of the specific heat production must lie, not within the absorptive or excretive mechanisms, but in the interplay between the living cells and the nutrient material, the sugars and amino-acids contained in the blood.

To determine the effect of sugars and amino-acids, experiments have been devised in which a dog was given a standard maintenance diet every evening, and eighteen hours thereafter, when the gastro-intestinal tract was free from food, the *basal metabolism* was measured. In Dog 3, on which eighty-two experiments have been performed, the basal metabolism was determined at different intervals and averaged 16.7 calories per hour. It scarcely varied from this during a period of nearly three months.

The effect of a substance to be tested was measured by giving it eighteen hours after the standard diet and noting the change which took place from the normal basal metabolism.

THE METABOLISM OF CARBOHYDRATES

After 50 gm. of glucose the heat production rose in one of the hourly periods to a maximum of 32 per cent. above the basal level. After 70 gm. of glucose a maximum rise was 38 per cent. With 50 gm. of fructose a similar rise was 44 per cent. and with 50 gm. of sucrose one of 48 per cent. Here then are very large increases. It has been shown on another occasion that 50 gm. of glucose are absorbed into the blood and disappear from the gastro-intestinal canal from three to four hours after its administration. At first the sugar-content of the blood increases, but then quickly falls to its normal percentage as the blood becomes more dilute, the latter fact being indicated by a fall in hemoglobin percentage. This greater volume of blood bears a greater number of readily

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diffusible molecules of sugar to the active tissues of the body. Following the end of the absorption of glucose, the kidney eliminates a large volume of the water which has caused the dilution of the blood, hemoglobin returns to its normal percentage, and the composition of the blood is again regulated by the liver and other organs through which it flows. In consequence of this, the heat production of the fourth or fifth hours after the ingestion of glucose regains the level of the basal metabolism. Those older experiments, which were performed during twenty-four-hour periods, do not show the very great temporary rise in metabolism after glucose ingestion, since calculations based on a long interval of time give no idea of the real state of affairs. Grafe's recent work on dogs which were overfed on carbohydrates throughout the day shows large increases in metabolism, as high as 33 per cent. above the level of an eighth day of fasting. This is fully explained in the light of the results given above.

But what is the cause of the increased heat production after the ingestion of sugar? On a former occasion I stated that it was due to the mass action of the sugar-molecules reacting with the living cells.

One might argue that this increased heat production is due to a breaking up of sugar in the inert fluids of the body and not in the cells themselves. An analogy is found in the living yeast-cell in which the greater part of the destruction of sugar is accomplished within the cell, itself, and a minor part in the surrounding fluid (Rubner). Recent work, however, has shown that the blood-plasma contains no glycolytic enzymes and cannot accomplish the breakdown of sugar.

Another explanation is offered by F. G. Benedict, who declares that acids formed in the intermediary metabolism of sugar are stimuli to increased metabolism. In substantiation of this, Benedict cites an instance of increased heat production following the administration of 100 gm. of fructose to a diabetic

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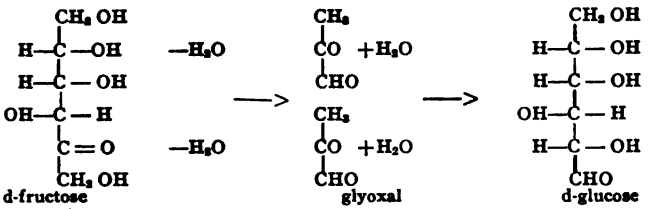
patient, by whom this sugar was not oxidized, but in whom it was converted into glucose and eliminated in the urine. Benedict interprets this as due to the breaking up of fructose into acid and other radicals which are subsequently synthesized into glucose. Modern theory indicates that methylglyoxal is the principal intermediary substance in this transformation. Benedict's experiment was of such interest that it has been repeated, using phlorhizinized dogs, but it could not be confirmed. The diabetic animal did not oxidize the fructose; it also transformed fructose into glucose, but the metabolism was in no way increased.

The transformation of glucose into levulose may thus be written:



If this transformation takes place through methyl glyoxal, which is also believed to be an early metabolism product of glucose, then when a molecule of glucose breaks and forms two molecules of methyl glyoxal, these small three-carbon aldehyd radicals cannot, through their presence, place metabolism on a higher level. But through their mass action on the living cell, the oxidative processes involved in their destruction may cause metabolism to reach this higher level. This is the metabolism of plethora.

Experiments have also been made with alcohol alone and with alcohol and 50 gm. of glucose. When 9.4 gm. of alcohol were given alone, the heat production of the dog was increased 10 per cent. When alcohol was given with glucose the heat production was raised above the level to which glucose alone would have caused it to rise, and alcohol was oxidized in prefer-

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ence to carbohydrate as shown by a marked depression of the respiratory quotient. Here the alcohol, with its small molecule containing only two carbon atoms, proved to be the more available fuel.

METABOLISM OF AMINO-ACIDS

Dakin states that nine of the seventeen amino-acids which make up the composition of protein yield glucose when they are broken up in the body. Glycocoll with two carbon atoms and alanin with three are completely convertible into glucose, and the ammonia produced in this transformation forms ammonium carbonate in the blood, which, in turn, is converted into urea. These reactions are *endothermic,* that is to say, heat is absorbed in order to produce sugar and urea. In the transformation of 20 gm. of glycocoll into 16 gm. of glucose and 8 gm. of urea 17.1 calories are absorbed. When 20 gm. of alanin undergo this transformation, 3.6 calories are required. The amino-acid known as glutamic acid contains five carbon atoms, three of which are convertible into glucose. These three amino-acids have been extensively used in the experiments to be described, which were devised in order to interpret the cause of the very great increase in the heat production which follows the ingestion of meat.

A striking point is that if 20 gm. of glutamic acid be given to a dog there is no increase whatever in the heat production of the animal. Twenty gm. of glutamic acid yield 13 gm. of sugar which, of itself, is too small to increase the production of heat. This amino-acid which is convertible into sugar and urea may be given without appreciable change in the heat production. If, however, 20 gm. of glycocoll be given, a very great increase in heat production follows. The higher metabolism lasts for seven hours. Twenty gm. of glycocoll containing 40 available calories increases the heat production by 30 calories during this period. This is greater than the 17 calories absorbed in the

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intermediary production of sugar and urea. Ten gm. of glycocoll produce just half the effect which 20 gm. accomplish.

Twenty gm. of alanin, containing 73 available calories, increases the production of heat by 20 calories, and 30 gm. of alanin cause an increase of 30 calories. The result which follows administration of the amino-acids is like that which occurs after meat ingestion, in that the amount of the increase is proportional to the quantity of material metabolized.

What is the cause of these great increases in heat production? Twenty gm. of glucose may have no effect whatever on the heat production, and 70 gm. may cause an increase of 20 calories, yet 20 gm. of glycocoll, which is convertible into only 16 gm. of glucose, raise the heat production by 30 calories, a height that 70 gm. of glucose cannot bring about.

What is the reason?

At the International Congress of Hygiene and Demography, held in Washington, I presented the view that it was due to the stimulation of the protoplasm to higher activity through the mass action of accumulated amino-acids. Folin had shown that amino-acids were quickly absorbed and were retained by the tissues, and he believed that their metabolism was of slow development, none taking place in the first hour. Experiments which have since been instituted have led me to believe that the highest heat production is coincident with the highest metabolism of amino-acids and that the amino-acids themselves do not lie in the tissues without being involved in a highly active metabolism. A year ago, Miss Wishart performed experiments on dogs killed in the height of excessive protein digestion, and failed to find any great increase in the quantity of non-protein nitrogen in the muscles. Another convincing reason of the rapidity of the metabolism of amino-acids, such as glycocoll and alanin, lies in the speed with which Csonka found that the sugar derived from them is

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eliminated in phlorhizin glycosuria. If 20 gm. of glycocoll be administered to a diabetic dog, 16 per cent. of the sugar derivable from it is eliminated in the urine of the first hour. At the end of five hours, 86 per cent. of the sugar which could be derived from glycocoll metabolism has been eliminated. The elimination of the sugar is almost as rapid as when a comparable quantity of glucose is given to the dog. The point to be emphasized is that this method of determining the rapidity of the metabolism of glycocoll and alanin shows that the early hours of their highest metabolism is coincident with the maximum increase in the production of heat within the dog after their ingestion.

After all, might not the great rise in metabolism be due to the oxidation of glycocoll or alanin as so much refuse which cannot be used as fuel for the cells? To determine this, glycocoll and alanin were given to the dog in the diabetic condition and the metabolism was measured. The heat production rose in both instances. Since the amino-acids were not oxidized but were eliminated as sugar and urea in the urine, the increased heat production must have been due either to the stimulus exerted by them on the living protoplasm or to the stimulation produced by the oxy- or keto-acids formed from them during their transformation into sugar.

That specific intermediary acids formed in metabolism are the real stimuli is indicated by the fact, first shown by Rubner, that when ingested protein is reconstructed into body protein the amino-acids involved in this reaction do not cause an increase in the heat production.

It does not seem probable, however, that this stimulation is induced by all acids, for the strong dibasic glutamic acid is without effect. It may be that lactic acid derived from alanin and subsequently converted into glucose is an effective stimulus, whereas methyl

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glyoxal, which is a problematic cleavage product of glutamic acid and is convertible into sugar, may not be an effective stimulus to higher oxidation.

In phosphorus poisoning, which is accompanied by formation of lactic acid, the total heat production is above the normal, although a high protein metabolism may here also be an accessory factor. In high altitudes, where lactic acid is always produced, metabolism increases.

The rise in heat production in diabetes may be partly induced by the great increase of fat in the blood and by the increased protein metabolism and not entirely by the diabetic acidosis as suggested by Benedict. For, in the dog, diabetic acidosis plays a very subsidiary part and yet an increase in the metabolism of the fasting phlorhizinized animal of 75 per cent. above the level of the basal metabolism has been noted.

Even though the cause of the increased heat production after protein ingestion be due largely to a stimulation caused by the presence of certain oxy- or keto-acids, yet the metabolism induced thereby can be defined as the metabolism due to amino-acid stimulation, to contrast it with the metabolism due to plethora in the presence of food molecules in abundance.

In conclusion, it may be stated that living cells metabolize carbohydrates and fats in increased quantity when these are present in large amounts in the surrounding fluid, and that they are also stimulated to a higher heat production during the metabolism of certain amino-acids to an extent which is entirely out of proportion to the energy value of those amino-acids, and which may indeed be independent of their energy value.

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THE TOTAL ENERGY REQUIREMENT IN DISEASE

AS DETERMINED BY CALORIMETRIC OBSERVATIONS*

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NEW YORK

The total energy requirement of an individual is represented by his heat production or, in other words, his total metabolism. If food of a total caloric value equaling the heat production be taken, the normal man will remain in nutritive balance. As a rule, the appetite in health regulates the intake to a nicety, although some of us need the guiding influence of the bathroom scales and the restraining influence of tight clothes. In disease, on the other hand, the appetite is no index of the requirement and the nutrition of the cells is at the mercy of the physician. Likewise, the stomach and kidneys are at his mercy, and he must regulate the diet so that it will nourish the cells without throwing too much work on damaged organs or oxidative functions of the body. It is often just as important to know the proper dosage of foods as to know the proper dosage of drugs.

The most satisfactory instrument for measuring the heat production is the respiration calorimeter[1] of the type devised by Atwater and Rosa in Middletown, Connecticut. Such a calorimeter, modified for clinical purposes, has been constructed by the Russell Sage Institute of Pathology in the wards of the Second Medical Division of Bellevue Hospital. Since its completion a year and a half ago, it has been used in 142

* From the Russell Sage Institute of Pathology in affiliation with the Second Medical Division of Bellevue Hospital.

1. Atwater and Rosa: Description of a New Respiration Calorimeter, 1899, Bull. 63, U. S. Dept. of Agr. Benedict and Carpenter: Respiration Calorimeter for Studying the Respiratory Exchange and Energy Transformations of Man. Carnegie Instit. Wash., 1910, Pub. 123.

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observations. A number of normal controls have been studied, but most of the subjects have been patients from the adjoining metabolism ward in which all diets are weighed and analyzed. This ward is under the control of the institute and those in charge of the calorimeter.

On the morning of the observation a patient, usually without his breakfast, is placed within the calorimeter where he remains for three or four hours. He finds himself on a comfortable bed in a well-ventilated box about the size of the lower berth of a sleeping-car. He can amuse himself by looking out of the windows, but since the scenery is monotonous he usually dozes for about half the time and allows his mind to vegetate for the other half. Absolute rest is essential, and the only movements permitted are those connected with turning in bed from time to time. All such movements are registered automatically by a device which is delicate enough to record even the small amount of work done by a man in stroking his mustache.

As the subject lies in the calorimeter the oxidation of the various foodstuffs within his tissues produces a certain amount of heat each hour. Approximately three-fourths of this heat leaves the surface of the body by means of radiation and conduction. This heat is removed from the calorimeter by a system of cooling pipes and is accurately measured by electrical thermometers. About one-fourth of the heat is removed from the body by the vaporization of water from skin and lungs. This water vapor is caught and measured in a sulphuric acid bottle.

If the body temperature should rise, it is obvious that some of the heat produced would be stored in the body itself and not eliminated. The estimation of this heat in short periods is a matter of great technical difficulty since the changes in rectal temperature, which are recorded every four minutes by means of a very accurate electrical thermometer, may not represent the average temperature changes of the

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body. Other thermometers strapped in the axillae and on the surface of the thorax or abdomen demonstrate that the different parts of the body show temperature curves which are by no means parallel, and that one part of the body may even be cooling while another part is warming. If the body temperature of a man of average size rises 0.5 degree centigrade it means that from 25 to 30 calories have been stored in the body in addition to the calories eliminated from the body. Such large changes, amounting to one-fourth or one-third of the total heat production for an hour, have been observed within an hour, and it is obvious that any inaccuracy in the determination of the average body temperature causes an error in the method of direct calorimetry. While the error may be large in a single hourly period, it becomes very small in an observation lasting three or four hours and seldom exceeds 5 per cent.

The heat production is measured not only by this method of direct calorimetry but also by the more accurate method of indirect calorimetry. The box is ventilated by a rotary fan which sucks the air out of one end of the chamber, drives it through a bottle of sulphuric acid to remove all moisture, then through a bottle of soda lime to remove the carbon dioxid and finally returns the same air, absolutely pure and odorless, to the other end of the calorimeter. As the patient uses up oxygen, this gas is supplied automatically from a small tank. By weighing these various bottles and tanks at the beginning and end of each hour it is a simple matter to determine the carbon dioxid produced and the oxygen consumed. Knowing the relative proportions of these and also the nitrogen of the urine one is able to calculate with great accuracy the grams of protein, fat and carbohydrate oxidized by the patient during that hour. Knowing the heat produced by the oxidation of 1 gm. of each of these substances it becomes a simple matter to calculate the total heat production.

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The two methods of direct and indirect calorimetry agree within 5 per cent. in about three-fourths of the experiments, and in many cases the figures are almost identical as is shown in Chart 1, that of one of the normal controls. In the total of all the experiments so far calculated, involving the measurement of 23,000 calories, the two methods agree within 1.6 per cent. As yet no disease has been found in our somewhat limited series of observations in which there is any

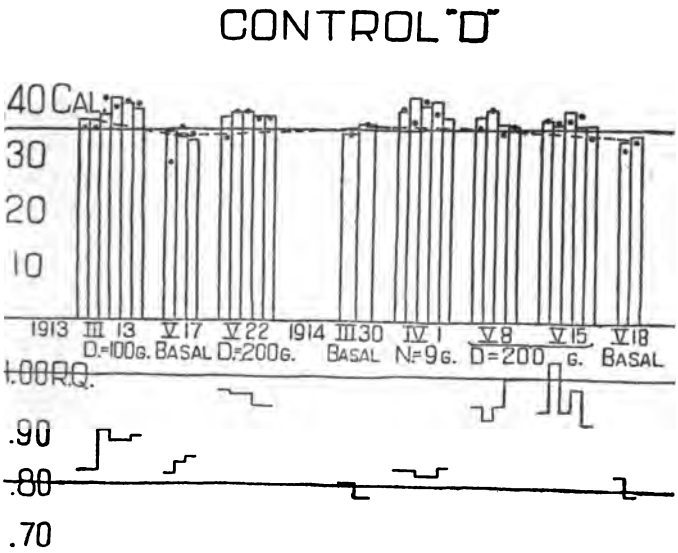

Chart 1.—Control D. Showing the basal metabolism in hourly periods and the effects of food in increasing the heat production. Each column represents the calories per square meter of body surface as determined by the method of indirect calorimetry. The round dot represents the calories as measured by the method of direct calorimetry. *D* stands for glucose; *N*, nitrogen in the form of casein and egg albumin. These were taken approximately one hour before start of observation except on March 13, 1913, when the glucose was taken after the basal metabolism had been determined in two one-hour periods.

consistent disagreement between the two methods. This is a matter of considerable import, since the previous work in the study of the heat production in disease has been done almost exclusively by the method of indirect calorimetry. The agreement of the two methods shows that the calculations by indirect calor-

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imetry have not been vitiated by any profound and unsuspected changes in the intermediary metabolism.

It is comparatively easy to determine the total metabolism but difficult to find the exact normal figure with which to compare the results. We have measured the basal heat-production of a number of normal persons of varying weights and have grouped them with the normal controls examined by Benedict in his bed calorimeter, all determinations being made on individuals at complete rest, from fourteen to sixteen hours after the last meal. It will be seen in Chart 2 that if we express the metabolism in terms of calories per square meters of the body surface per hour, the results will group themselves close to the average figure of 34.2 irrespective of the body-weight. The dotted line represents the average of forty-nine normal controls studied by various types of apparatus in many laboratories. It is evident that the level is the same for persons whose weights are between 40 and 50 kg. (from 88 to 110 pounds) as for those whose weights are between 60 and 70 kg. (from 132 to 154 pounds). On the other hand, if we express the results in terms of calories per kilogram per day we have a line of averages which falls steadily as the weight increases. In order to have a single base-line which need not be changed for persons of varying weights we therefore compare all our results with the average normal figure of 34.2 calories per square meter per hour.

While the metabolism of a given individual remains fairly constant for years, there may be a variation among normal men of 10 per cent. above or 10 per cent. below the average. Further study will perhaps show even a greater variation. The metabolism is increased in childhood, diminished in old age, and probably depends, to a great extent, on the nutrition of the body and the mass of active protoplasm. Nevertheless, Rubner's law that the metabolism of different individuals and different species of animals is proportional to surface area does hold good within cer-

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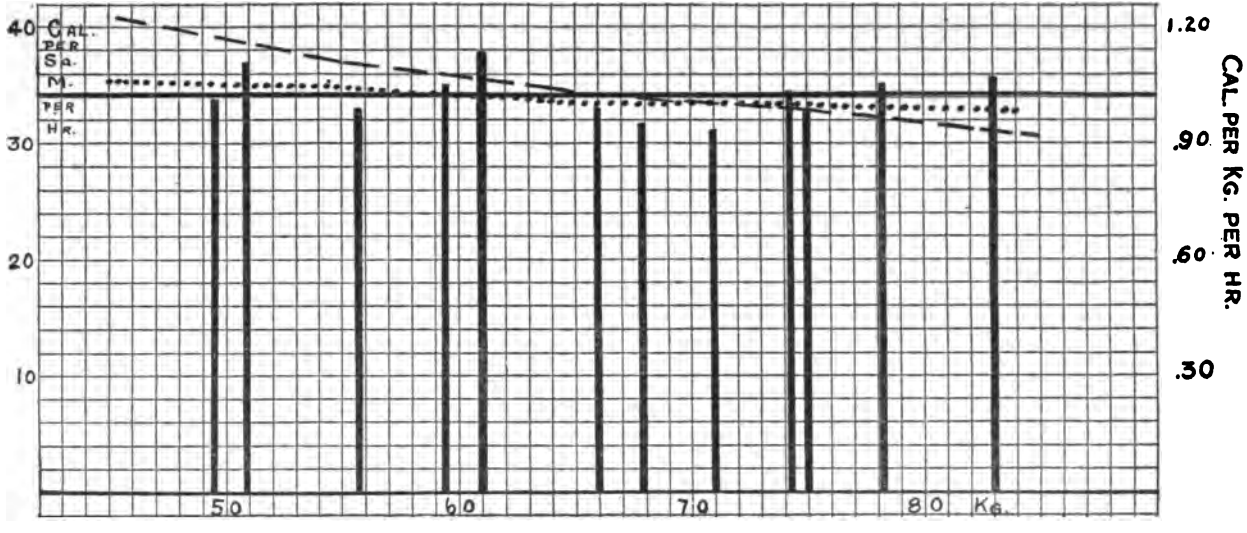

Chart 2.—Basal metabolism of normal men from fourteen to sixteen hours after the last meal. Columns represent calories per square meter per hour produced by subjects in bed calorimeter. Horizontal line drawn at 34.2, the average. Interrupted lines represent averages of 49 normal controls studied with various types of respiration apparatus, arranged in five groups according to weight. Dotted line shows the results expressed according to surface area. Dash line represents the same 49 controls with the results expressed in terms of calories per kilogram per day.

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tain limits. These limits may be wide when we try to compare the metabolism of babies, guinea-pigs, athletes and fat men, but, as we have shown above, the limits are narrow for a group of men of approximately normal build.

Voit and Rubner demonstrated the fact that the taking of food raised the heat production, and the term of specific dynamic action was applied to this phenomenon. The cause of this was little understood until Lusk[2] studied the matter in great detail, making hourly determination of the heat production of dogs in the small Cornell calorimeter. His work on dogs has been duplicated on normal men as nearly as the human stomach will permit, but, of necessity, the amounts of food are relatively smaller and the increases in heat production distinctly less marked. Chart 1 shows the basal metabolism of control D and the effects of glucose and protein meals. The increase after glucose amounts to from 8 to 10 per cent. and after protein to 12 per cent.

Since the time of Voit and Pettenkofer a great deal of work has been done on the subject of the respiratory metabolism and total heat production in disease. Magnus-Levy[3] established the fact that in exophthalmic goiter the energy requirement was greatly increased even to a point as high as from 50 to 70 per cent. above the normal and showed that in cretinism and myxedema the heat production might be as low as from 45 to 50 per cent. below the normal. Kraus,[4] Grafe,[5] Rolly[6] and others demonstrated that in typhoid fever the metabolism was raised to from 30 to 40 per

2. Lusk: Animal Calorimetry, Papers II, III, V, VI, Jour. Biol. Chem., 1912, xii, 349; xiii, 27, 155, 185; Cause of the Specific Dynamic Action of Protein, Arch. Int. Med., December, 1913, p. 485; The Specific Dynamic Action of the Foodstuffs, this issue, p. 824.

3. Magnus-Levy: Gaswechsel bei Thyroiden, Berl. klin. Wchnschr., 1895, xxxii, 650; Ueber Myxödema, Ztschr. f. klin. Med., 1904, lii, 201.

4. Kraus, Fr.: Ueber den respiratorischen Gasaustausch im Fieber, Ztschr. f. klin. Med., 1890, xvi, 160.

5. Grafe: Untersuchungen über den Stoff- und Kraftwechsel im Fieber, Deutsch. Arch. f. klin. Med., 1911, ci, 209.

6. Rolly: Experimentelle Untersuchungen über den Stoffwechsel im Fieber und in der Rekonvalescenz, Deutsch. Arch. f. klin. Med., 1911, ciii, 93.

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cent. above the normal. Grafe[7] has recently shown that the heat production is low in certain stuporous conditions and increased in lymphatic leukemia and cancer. The total heat production in diabetes has been studied by many observers with varying results, but Benedict and Joslin,[8] using the calorimeters in Boston, have shown that in cases of severe diabetes with acidosis there is an increase in metabolism.

The study of the metabolism in typhoid fever and the effects of the high-calory diet was begun in Bellevue Hospital in 1911 in association with Dr. Warren Coleman. The small Benedict apparatus was used and the calculations were made according to the method of indirect calorimetry. A summary of the results will be presented by Dr. Coleman[9] in another Section but it may be stated that the heat production of the patients was not raised by the administration of large amounts of food during the height of the fever. The matter seemed so important that it demanded investigation by the use of the calorimeter.

Observations were therefore made on nine typhoid patients during the course of the fever and convalescence. The first part of the results on one patient, who was in the calorimeter twenty-two times, is shown in Chart 3. This patient enjoyed the work with the calorimeter. His original infection was by no means mild and he had one relapse which was severe and a second relapse which scarcely interrupted a rapid convalescence. Throughout the disease he was so well nourished that his weight remained practically constant.

7. Grafe: Beiträge zur Kenntniss der Stoffwechselverlangsamung bei stuprösen Zuständen, Deutsch. Arch. f. klin. Med., 1911, cii, 15; Die Steigerung des Stoffwechsels bei chronische Leukaemie und ihre Ursachen, Deutsch. Arch. f. klin. Med., 1911, cii, 406; Das Verhalten von Gesamtstoffwechsel und Eiweissumsatz bei Karzinomatösen, Deutsch. med. Wchnschr., 1914, xl, 518.

8. Benedict and Joslin: Metabolism in Diabetes Mellitus, Carnegie Inst. Wash., 1910, Pub. 136; A Study of Metabolism in Severe Diabetes, 1912, ibid, Pub. No. 176.

9. Coleman, W.: The Effects of Food on Metabolism in Typhoid Fever, read in the Section on Pharmacology and Therapeutics at the Sixty-Fifth Annual Session of the American Medical Association, Atlantic City, N. J., June, 1914.

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It will be noticed that during the fever his total metabolism was from 40 to 50 per cent. above the average normal and that it was scarcely increased at all on the days when the observations were made shortly after the ingestion of 100 gm. of glucose or 64 gm. of protein. A study of the nitrogen in the urine in this and three other cases shows that the percentage of calories derived from protein during fever

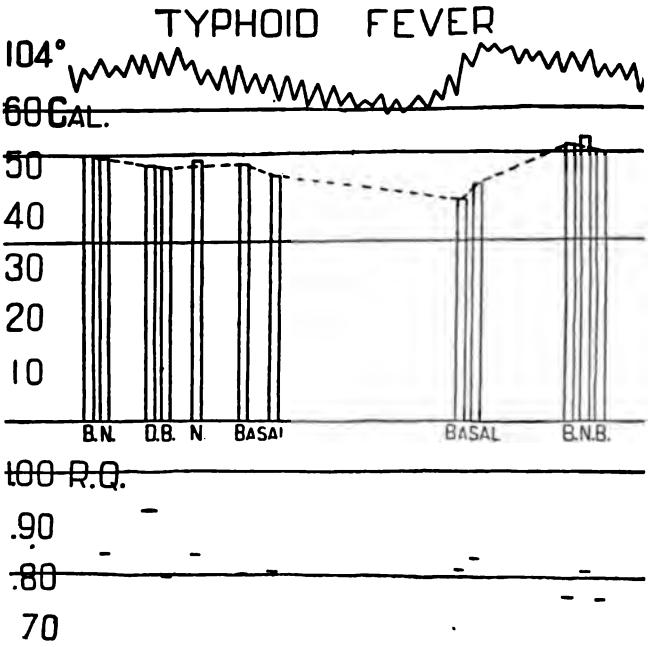

Chart 3.—Typhoid fever, "Morris S." Basal determinations, *B* connected by dash line. *N*, protein meal. *D*, from 100 to 200 gm. of glucose. Results expressed in averages.

when the patients were fasting was seldom raised above the upper normal limit of 20 per cent., although one patient early in his disease derived 28 per cent. of the calories from protein.

As the temperature falls the total metabolism diminishes and the percentage of calories derived from protein drops to 10 or 15 per cent. During convalescence heat production may be from 20 to 30 per cent.

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above normal, and at this stage glucose and protein exert as great a specific dynamic action as in health.

The diseases of the thyroid gland have been studied with particular interest since the level of the total metabolism seems to be the best index of the activity of the thyroid secretion. In one cretin who was 36 years old but had the mental and physical development of a child of 8, the total energy requirement was from 18 to 25 per cent. above the normal but was raised almost to the normal on the third day of treatment

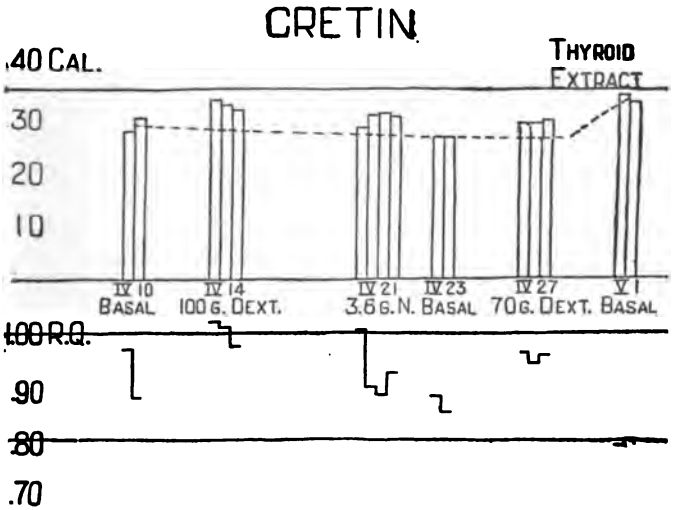

Chart 4.—Cretinism results expressed in hourly periods. Thyroid-extract treatment begun two days before last observation.

with thyroid extract (Chart 4). The specific dynamic action of food was normal in this patient.

A series of seven patients with exophthalmic goiter were studied before and after treatment in an effort to guide the therapeusis in this disease, which is remarkable for the number of "remedies" that do not give relief. Luckily we were able to show some beneficial effects of treatment, although good results were obtained by rest and careful feeding alone. One patient, who had shown moderately severe symptoms

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for one year, was studied over a considerable period of time. If we look at the results as expressed in Chart 5, we notice that, in marked contrast to the cretin, the metabolism is 80 per cent. above the normal, falling to 60 per cent. on rest and good food. Von Noorden[10] has stated that the specific dynamic action of food and especially of meat is increased in fever and in exophthalmic goiter. We have seen that this

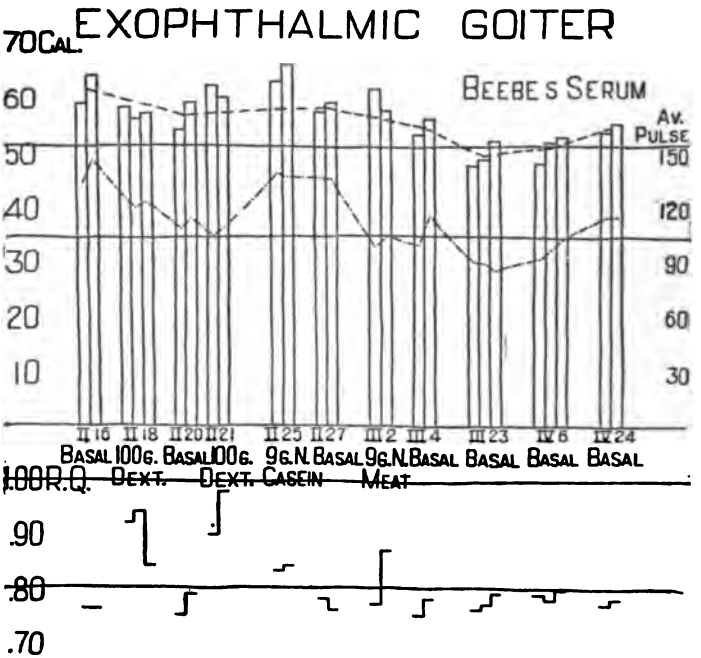

Chart 5.—Exophthalmic goiter. Results shown in hourly periods. Dash line connects basal determinations. Dot-dash line represents average pulse during the period of observation in calorimeter.

was not the case in fever and it was evidently not true of this patient, since his metabolism was not raised even so much as that of a normal man by glucose, casein and meat. After treatment by Dr. S. P. Beebe with his antithyroid serum, there was a distinct improvement in the man's condition and fall in the

10. Von Noorden: New Aspects of Diabetes, New York, E. B. Treat & Co., 1912, p. 20.

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metabolism. After the first month there was a rise in metabolism to its former level but the general improvement continued perhaps, however, at a slower rate.

A young woman who was up and about, though not quite able to continue her work as trained nurse, showed the extraordinarily high metabolism of 92 per cent. above the normal. After ligation of the arteries by Dr. John Rogers, the metabolism fell to 60 per cent. above the normal and the patient's condition was distinctly improved.

One young woman with a mild case of the disease showed a marked rise in metabolism four days after ligation of the four thyroid arteries, indicating that the operative procedure had temporarily increased the activity of the gland. Later there was distinct improvement in her general condition and a fall in the heat production to its former level.

Other conditions have been studied in a few cases and while the results need confirmation, they are suggestive and may lead to a better understanding of the various factors which influence the heat production in disease. One patient with splenic anemia, whose hemoglobin was 25 per cent., had a metabolism 11 per cent. above the normal; another with pernicious anemia for which a splenectomy had been performed, showed an increased metabolism amounting to 20 and 26 per cent. above the normal, while his hemoglobin was only 20 per cent. This confirms the older work, which demonstrated that there is no diminution of oxidation as a result of the low percentage of hemoglobin. In a patient with nephritis a change in blood-pressure from 195 to 160 caused absolutely no change in heat production. One man with acromegaly had a metabolism 18 per cent. above the normal, another with symptoms of deficiency of the secretion of the posterior lobe of the hypophysis gave results sometimes high and sometimes normal but he was so stupid that he made a very unsatisfactory subject. Another man

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with malaria was studied at the height of his fever, and also six days later when his attacks were cured. With a temperature of 104 F. the metabolism was 83 per cent. above the average, with a normal temperature, 21 per cent. A patient with auricular fibrillation, mitral stenosis and greatly enlarged heart but without orthopnea, was observed three times lying flat on his back and twice propped up with a back-rest. We were astonished to find the metabolism which was normal when he was propped up was 8.5 per cent. higher when he was lying down and were even more surprised to observe the same phenomenon in the only normal control we studied in this posture.

The increases due to fever, hyperthyroidism and the like, are probably small compared to the increase caused by muscular work in delirium tremens or convulsions. Even slight restlessness or mild excitement causes a rise in heat production which is distinctly appreciable in the calorimeter.

In conclusion, it may be well to emphasize the fact that the nutrition of a patient depends absolutely on the relationship between his energy production and his food-supply. If the organism fails to obtain food from without it will draw on its own glycogen stores, fat depots and supplies of body protein.

129 East Seventy-Sixth Street.

ABSTRACT OF DISCUSSION

ON PAPERS OF MENDEL, FOLIN, LUSK AND DU BOIS

Dr. S. J. Meltzer, New York: For more than thirty years I have been moving on the periphery of laboratory work on one side and clinical medicine on the other side. Well do I remember the wide gulf which separated the laboratory men from the men in clinical medicine. To-day we have heard four men telling of their work in the sciences of medicine and telling it to a large audience, consisting, as far as I can judge, chiefly of men who are active in the practice of medicine. There are reasons for more congratulations. We heard to-day four men telling of their own original work in the scientific part of medicine. In the times gone by the laboratory man was satisfied to discuss work which was done on the other side of the Atlantic; to-day the scientific men in Europe take

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profound notice of the work done in this country. Again, in the past, laboratory men used to be proud of the fact that they had nothing to do with the practice of medicine. To-day the laboratory men are anxious to do work in fields which are of special interest to the practitioner. Mendel speaks of "gaps and guesses" in scientific reports. I am certain that a thousand years from now "gaps and guesses" will have a prominent place in scientific reports. The gaps which we fill out by our investigations, we do by means of guesses, and they reveal to us new gaps. Liebig's theories are mere guesses for us to-day, to be forgotten. But they were instrumental in filling up many gaps by facts. Theories are of value because they help us to discover facts, and as long as they can do that they are still of value to us. I wish to say to Dr. Mendel that the amboceptor theory of Ehrlich, of which he spoke somewhat disparagingly, has brought out thousands of important facts in immunity, and is still capable of bringing out new facts. I am still more sorry that Dr. Mendel spoke in a somewhat disparaging manner about salvarsan. The synthetic creation of such a specific substance like salvarsan is one of the most wonderful discoveries made in recent times in the sciences and practice of medicine. The discovery by Dr. Mendel in conjunction with Osborne, that butter does contribute to the growth of rats, while lard does not do it, is perhaps the best he has ever made. This discovery was made by the empirical method; they do not tell us on what hypothesis they found it; neither what is the nature of the "vitamin" which differentiates lard from butter. We call this method, when used in science, the inductive method. But it differs from the empirical method which the physician uses merely by the application of criticism. Criticism is here necessary to differentiate the coincidental from the causal connection. Here the physician must learn from the scientist. A patient may get better merely while he is taking a drug and not because he takes it. But there is one point which the scientist has to learn from the physician; it is the principle of *non nocere;* be sure that you do not do any harm. For instance, the knowledge that the minimum diet is of no perceptible immediate harm to animals is no evidence that it will be of no harm, acute or chronic, to human beings. Neither do we know that infants will behave like rats regarding the difference between butter and lard.

Dr. F. M. Pottenger, Los Angeles, Cal: Does this difference in the absorption of fats apply to all animals alike, whether herbivorous or carnivorous and also to man?

Dr. E. P. Joslin, Boston, Mass.: I should like to ask Dr. Lusk if he has an explanation to offer as to why the metabolism is not increased by food in typhoid fever?

Dr. Allan Eustis, New Orleans: I wish to discuss that part of the subject in which Dr. Mendel refers to the amins

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formed by the putrefaction of the several amino-acids in the intestinal tract. This has a broad practical application in clinical medicine, as each of these amins has its own specific physiologic action, just as the amins from the vegetable kingdom, represented by the alkaloids strychnin, morphin, etc. Tyramin (para-oxyphenylethylamin), which is yielded by tyrosin on putrefaction, is capable of raising the blood-pressure in a dog from 110 to 250 mm., while in man it has produced a rise to 180 mm. I have made application of this fact in treating nearly five hundred cases of arterial hypertension, in which the systolic blood-pressure has been kept down to 140 or 150 mm. by dietetic means alone. It must be remembered that caseinogen of milk yields 7 per cent. of tyrosin on digestion which contra-indicates milk as an ideal food in this condition. Inasmuch as all animal proteins yield large amounts of tyrosin they are also contra-indicated, while the best results will be obtained from a cereal and fruit diet. The clinical application of the formation of histamin (beta-imidazolylethylamin) from histidin can be made in the treatment of bronchial asthma and urticaria. When injected intravenously, this amin causes violent bronchial spasm similar to an attack of asthma, while when rubbed vigorously into the skin a solution of 1:1,000 causes a typical urticarial lesion. Along dietetic lines alone, I have been able to give relief in 168 cases of bronchial asthma and twenty-six cases of urticaria, some of the asthmatics having had the disease for twenty years. A diet for these conditions should be based on the fact that the yield of histidin in the more common types of proteins is: hemoglobin, 10 per cent.; sturin, 12 per cent.; caseinogen, 2.5 per cent.; 2.5 per cent., and gliadin, 1.4 per cent. Articles of diet which yield little or no hisidin may be allowed. It must not be concluded that all cases of arterial hypertension are due to the absorption of tyramin from the intestinal canal, nor that all cases of asthma and urticaria are due to histamin absorption; but it must be admitted that these amins have a decided practical bearing in clinical medicine and must be reckoned with.

Dr. Douglas Head, Minneapolis: I should like to ask whether any observations have been made as to the effect of butter feeding on heat production in long, thin-chested, enteroptotic persons as compared with those of short, stocky build?

Dr. A. J. Carlson, Chicago: I think you all know that in this particular field America has made a distinct contribution to science. I have been impressed by the interest taken in this symposium by the members of the American Medical Association. If there is anything new of importance in the practice of medicine it is this modern work in nutrition. And it is evident that when the laboratory men really have something to say the clinical men will listen.

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Dr. Victor C. Vaughan, Ann Arbor, Mich.: Will Dr. Folin explain one point on which he did not touch? We recognize that in enterodigestion the proteins are split into amino acids. Dr. Folin holds that the amino acids are absorbed directly into the walls of the intestines, a view held by many others. The proteins are carried to each cell and each cell utilizes what is suited to its needs. This I dare say is all right. One point which he should explain, is important. There must be some synthesis of amino acids in the body. The sero-albumin and globulin in the blood are specific proteins, each coming from different sources. These are taken into the blood, and by the brilliant work of Folin and others we are now able to demonstrate the presence of amino acids in the body. Now there must be some synthesis somewhere. We must not lose sight of the fact that enterodigestion is not the only form of digestion that occurs in the animal body. There is in the blood a digestive process as much as in the intestines. A proteolytic ferment is present in the blood, a trypsin and an antitrypsin, and the understanding and the adjustment of the relation of these two factors is one of the great problems of physiologic chemistry.

Dr. Otto Folin, Boston, Mass.: Undoubtedly all will agree that the question asked by Dr. Vaughan is too much for even a laboratory worker to attempt to answer. The question that Dr. Vaughan has really asked is "How are tissues formed?" I have discussed the subject of the destruction and the history of protein in the body from the point of view of food and from that of destructive metabolism. The matter has two aspects, a destructive and a constructive; the constructive or the synthesis of protein is synonymous with the formation of tissue itself and is far from the transformation of amino acids into urea. There are two distinct aspects of metabolism. I considered only the destructive processes, the breaking down, and these only as produced by the class of agents sometimes known as enzymes. Frequently enzymes are of the destructive variety. They are hydrolytic and there is a degradation form of reaction. As to the difference between the enzymes and the proteins and the subject of hydrolytic and synthetic ones, all can discuss this part of the subject as well as I can.

Dr. Graham Lusk, New York: Replying to Dr. Joslin's question, "Why is there no increased metabolism in typhoid fever after giving an excess of food?" I would call attention to the fact that under normal conditions the basal metabolism is measured by the heat production of a subject whose gastro-intestinal tract is free from food and who is living at an environmental temperature of 26 C. (78.8 F.). If, however, the temperature be lowered there is an increase in the heat production although, under these circumstances, the

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ingestion of food may now produce no specific dynamic action. Furthermore, it is known that, if the metabolism be increased to a certain point through carbohydrate, the addition of amino acids to the diet may cause no further increase in metabolism. Likewise, it should be remembered that in fever the protein metabolism can never be reduced to the low level present in the normal person, so that when amino-acids enter the organism under these circumstances they tend merely to replace those already breaking down in large quantity. It is therefore apparent why in fever the metabolism may have already been lifted to such a level that ingestion of food causes no further increase.

Dr. Eugene F. Du Bois, New York: A comparison of the metabolism of enteroptotic persons with that of short, stocky men would be interesting, but we have had no opportunity of making such observations. From a theoretical consideration it would seem that the enteroptotic, undernourished persons would have a rather low metabolism, and it would seem that muscular persons would have the higher metabolism. Yet from clinical observations it appears that the enteroptotic persons have the greater energy requirement. We have at times tried to guess the actual heat production of individuals and groups of patients but have found that sometimes we were as much as 25 per cent. from the true figures as determined by the calorimeter.

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THE HEART IN THE PNEUMONIAS

ROBERT N. WILLSON, M.D.
PHILADELPHIA

According to the vitality and endurance of the heart and the circulatory system (including its vasomotor supply), may be reckoned the outcome of the given instance of pneumonia. Seldom, if ever, will the mechanical obstruction of the lungs prove a serious factor except in its influence on an already crippled cardiac mechanism. The less perfect the aeration of the blood in its passage through the pulmonary tissue, the more positive is the deprivation of the cardiac structure (muscle, ganglion and nerve) of its proper supply of nutriment.

The importance of this influence is emphasized by the reflection that the blood, under conditions of health, demands over 90 per cent. saturation with natural oxygen as the result of its passage through the lungs.[1] The more complete the stoppage of the blood- and lymph-streams in their course through the walls of the air-vesicles, the more real is the mechanical overload thrown on the pulmonic valve, and soon on a toxemic, tired, right ventricular wall. The more intense and virulent the toxemia, the more certain and extensive will be the damage to the entire cardiac mechanism, vascular, nervous and muscular. Yet there is often to be noted at the necropsy table a surprising discrepancy between the severity of the pneumonic process and of the toxemia, and the apparent damage sustained by the heart.

Many observers have commented on the fact that the heart in certain virulent, fatal pneumonias may appear to be affected in surprisingly mild degree.

1. Cooke and Varcroft: Jour. Physiol., 1914, xlvii, 35.

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There may be little or no dilatation, no apparent incompetence of the valves, in short, seemingly no abnormality of a heart in a patient who has from the onset of the toxemia appeared to be doomed in spite of every effort to combat the disease. Such instances are practically always examples of intense, fulminant poisoning, in the so-called croupous or fibrinous type of the disease. The course is brief, the attack is largely on the nervous centers, and the heart, though always participating in the storm, seems to maintain a remarkable degree of power and equilibrium to the very end.

Not infrequently the microscope will reveal appreciable damage that escapes the naked eye. Clinically, as well as at the necropsy, however, the heart-muscle appears to be the last vital force to give way. Not so, in the many instances of bronchocatarrhal pneumonia, in which we practically never observe a sthenic patient or a heart which gives either clinical or post-mortem evidence of strength, stability or endurance.

One learns to associate the bronchocatarrhal type of pneumonia with a weak, dilated right heart, and on this basis very early to discriminate it from the croupous or fibrinous form of the disease. The temperature is irregular and low, the pulse running, rapid and often irregular, the patient asthenic far beyond the degree commensurate with the amount of pulmonary involvement—such is the clinical picture of the form of the disease in which the cardiac musculature and the vasomotor nervous system seem to sustain to such a preponderant degree the brunt of the attack. After such a pneumonia the post-mortem examination reveals almost invariably a flabby, characterless heart-muscle, of which incompetence is the main feature and dilatation the most meaningful expression. Routier[2] has recently reported a pneumonia in which the influence of the toxin on the fibers of the auriculoventricular conducting path resulted in a transient heart-block which disappeaared spontaneously. By no means

2. Routier: Arch. d. mal. du coeur, May, 1914.

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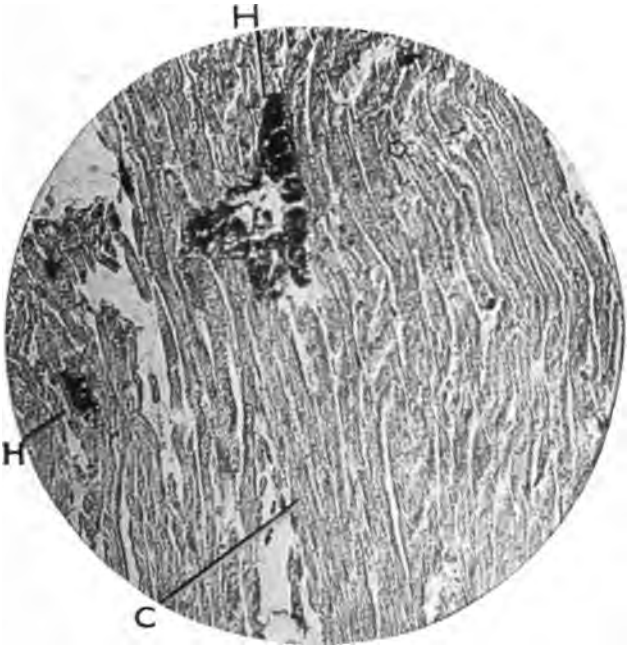

Fig. 1.—The heart-muscle in a case of croupous pneumonia, showing the rich capillary blood-supply to each fiber, the capillaries lying within (or in a groove in) the latter (*C*); interfibrillar hemorrhage (*H*), and complete loss of striae.

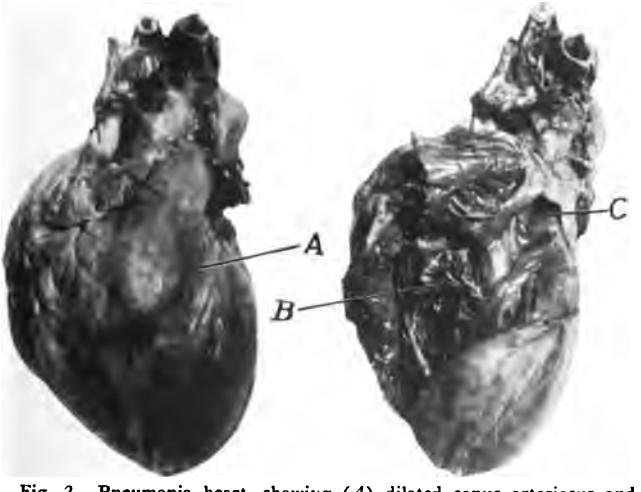

Fig. 2.—Pneumonia heart, showing (*A*) dilated conus arteriosus and right ventricle from without, and insufficient tricuspid (*B*) and pulmonic (*C*) valves.

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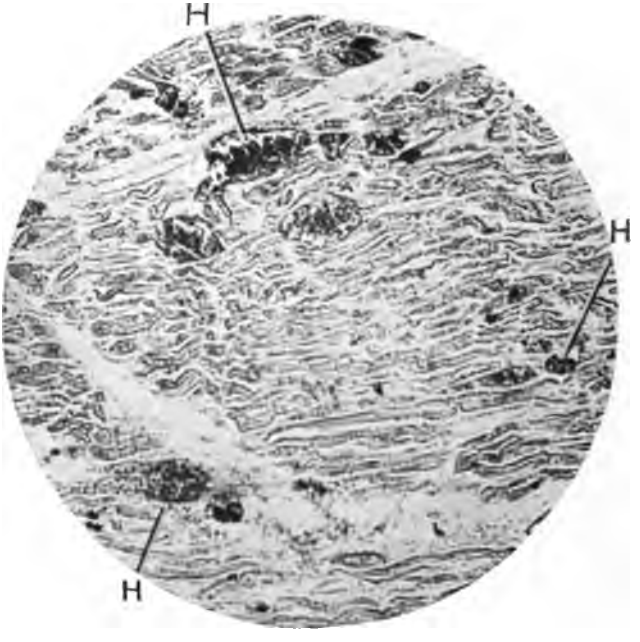

Fig. 3.—Heart-muscle from the left ventricle in a case of broncho-catarrhal pneumonia. Extensive degeneration of the fibers, with widespread hemorrhages (*H*). Striae completely lost.

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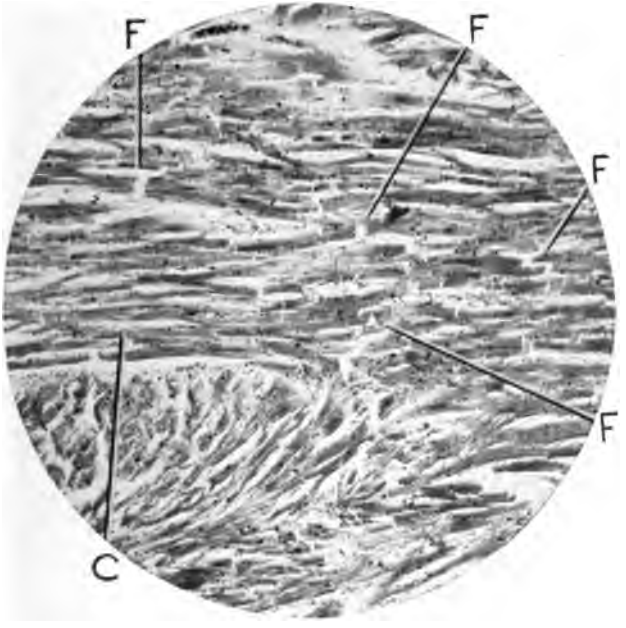

Fig. 4.—Heart-muscle in a case of bronchocatarrhal pneumonia. Striae show here and there, but have mostly disappeared. Considerable fragmentation of the fibers (*F*). The capillary blood-supply is beautifully distinct (*C*).

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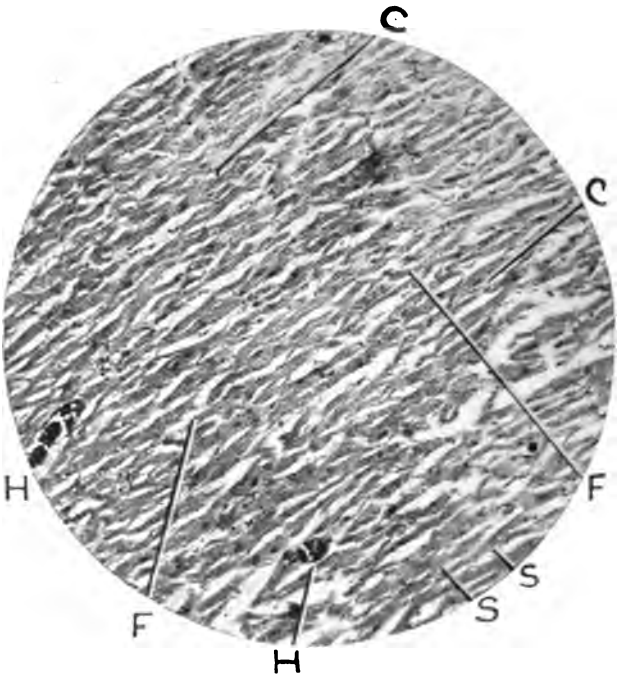

Fig. 5.—Heart-muscle in a case of bronchocatarrhal pneumonia, showing considerable atrophy of the fibers, scattered hemorrhages (*H*) and extensive fragmentation (*F*). Striae are seen here and there (*S*). Capillary blood-supply is exquisite (*C*).

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infrequently, however, the walls of both the left and right ventricles are thinned, and all of the valves, pre-eminently the pulmonic and tricuspid, are insufficient. I have one interesting specimen in my collection (Fig. 2) in which the conus arteriosus and the pulmonary artery both show marked permanent stretching and distention, the pulmonic valve appearing wide open between.

THE MICROSCOPIC CHANGES

I think it permissible to say that the heart shows post-mortem evidences of the toxemia in every fatal case of fibrinous, as well as of bronchocatarrhal pneumonia, that reaches the microscope. In the latter type of the disease the changes are more likely also to be macroscopic. I think it likely that every heart that weathers the pneumonic storm sustains similar lesions, of milder degree perhaps, yet from which it probably never fully recovers.

During the past year I have taken great interest in studying microscopic sections of the cardiac musculature from fatal cases of pneumonia in the wards of the Philadelphia General Hospital. In not a single instance was there a lack of evidence that a toxic influence had been actively at work. Usually the process appeared in the form of an acute diffuse myocarditis, with cloudy swelling of the cells, often with fragmentation of the muscle-fibers. In the great majority of cases the striations had nearly disappeared from the fibers, over wide areas, if not generally throughout the heart. Not infrequently could be found here and there areas showing extensive round-cell infiltration, mainly of the interstitial substance between the fibers. In quite a number of instances, as exemplified in Figure 3, there was wide-spread hemorrhagic infiltration. The nuclei of the muscle-cells were proliferated, were often swollen, and here and there vacuoles appeared in their place. Many of the muscle-fibers gave the appearance of being atrophied. In no case except in

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old persons, or in those afflicted with organic cardiac disease, was fatty degeneration of the heart-muscle observed.

Macroscopically as well as microscopically, there was evidence in every heart examined of some degree of pericarditis. I observed not one instance in over a year's time of fresh endocarditis, except such as was superimposed on an old lesion.

THE BLOOD-PRESSURE

Before using the blood-pressure as an evidence of either cardiac competence or insufficiency in the pneumonias, it is incumbent on us to show that in a sthenic pneumonia the customary or normal pressure is due to an overacting or at least a capable heart; while in the low-grade or asthenic pneumonias the low pressures are due to an incompetent cardiac mechanism rather than to vasomotor failure. The personal equation will of necessity enter largely into the verdict rendered by various investigators of this question. During the past three years I have studied more or less thoroughly over seven hundred cases of pneumonia on the wards of the Philadelphia General Hospital. Both with the finger on the radial, carotid and apical pulses, and with the sphygmomanometer, I have measured the blood-pressure in very many of these cases. I have a few records of the systolic pressure made in certain sthenic fibrinous pneumonia cases reading as high as 170 and 180 mm. of mercury. Far more often the readings followed approximately the normal line (from 120 to 140 mm.). I refer, of course, only to the active and sthenic stages of the toxemia. I have yet to see in a patient with pneumonia of the bronchocatarrhal type (except in childhood) an instance of high or even of normal systolic blood-pressure. Even in instances associated with symptoms of nephritis, or with arteriosclerosis of high grade, there has persisted a low systolic pressure, indicating insufficiency of cardiac vigor and driving power.

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The diastolic pressure, elicited by the auscultatory method, furnishes a fair index of the vasomotor tone. While this also is usually lowered in pneumonias of the asthenic type, it falls by no means in a measure commensurate or parallel with the cardiac power. Thus the systolic pressure in cases of bronchocatarrhal pneumonia during the stage of active toxemia has averaged not far above 100 mm., while the diastolic pressure has seldom registered below 80 mm., yielding an average pulse-pressure of 20.

This fact, together with such manifest indications of cardiac insufficiency as systolic jugular pulsation, arhythmia, small rapid pulse, enlargement of the area of cardiac dulness to the right, and often a series of valvular murmurs that can only be interpreted as indicative of muscular (relative) insufficiencies, apparently allow us but one possible conclusion, namely, that in the great number of low-grade pneumonias the heart-muscle must be ever an object of care and concern. Gibson[3] has called attention to a possible prognostic relation of the systolic cardiac pressure to the pulse-rate. Lauder Brunton has made a similar study of the diastolic pressure. In my own experience the systolic pressure has furnished a very uncertain prognostic index, for the reasons already stated. The majority of the low-grade pneumonias have presented a systolic pressure almost constantly lower than the pulse-rate, and yet the vast majority of these patients, when properly treated, have recovered.

THE INFLUENCE OF TREATMENT

Considerable evidence may be gained as to the actual condition of the cardiac mechanism through studying the results of treatment. It is a current belief and teaching, employed perhaps more freely than is justified by circumstances, that the pneumonic patient dies not of his pulmonary involvement, and not of his cardiac embarrassment, but owing to paralysis of the

3. Gibson: Edinburgh Med. Jour., 1908, lxv, 22.

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vasomotor system. In acute fibrinous sthenic pneumonia there would seem in certain instances to be at least some reason to support this view. In the bronchocatarrhal type of the disease there is exceedingly little. No better illustration could be given of the truth of this assertion than the fact that the high or normal blood-pressure in the fibrinous type appears to be due to overaction of a sthenic heart; while conversely, in the bronchocatarrhal form the asthenia and the almost invariably low blood-pressure appear to be due not nearly so much to loss of vasomotor tone as to actual cardiac dilatation and disability. Instances that admit of reestablishment of the cardiac tone do well. The most telling advantage seems to come from the systematic and thorough emptying of the intestinal tract, in many cases the manufactory of the toxic products. When the bowel has been deliberately rendered and kept clean the heart has, in my experience, seemed to have its best opportunity for rehabilitation. The moment the bowel has been neglected the heart has apparently suffered in a measure that is not to be explained on the basis of mere mechanical embarrassment. Such remedies as nux vomica, quinin, camphor, digitalis and oxygen in Nature's own form of warm, clean air, may serve as cardiac tonics and, on occasion, as indispensable temporary crutches. Under their influence the blood-pressure rises and may be maintained at a more favorable level.

On the other hand, such drugs as epinephrin and pituitary extract I consider dangerous in the presence of a weak heart. While they are certain to afford a momentary rise in the blood-pressure as the result of their influence on the vasomotor system, I have more than once seen evidence of their mischievous, and possibly lethal, action on a weak heart, through the imposition on its crippled musculature of an additional load in the form of a tense peripheral circulation. Nature knows better than we when to elevate and when to lower the intravascular tension.

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In a sthenic fibrinous pneumonia practically any treatment may be employed. We start and finish with the knowledge that in the vast majority of instances, otherwise healthy, non-alcoholic men and women should recover. Not so with the bronchocatarrhal, asthenic pneumonia patient, who must be supported actively through the disease because his vital forces, especially his cardiac mechanism, are all below par. Many a case of mistreated pneumonia takes on a totally different appearance when placed under conditions that favor and nourish instead of depleting the tone and strength of the heart. Perhaps the best illustration may be had in the misuse of cold air on an asthenic patient suffering from pneumonic toxemia. I have placed many such shivering, cyanotic subjects in warm, clean air and witnessed the immediate reestablishment of forces that were fast beginning to wane. Uppermost and most striking of all appeared to be the influence on the heart, which craved oxygen as its natural stimulant and tonic, but needed it in the form of warm, as opposed to cold, clean air.

PREEXISTING CARDIAC DISEASE

A final bit of evidence as to the importance of a thoroughly healthy cardiac mechanism — including musculature, valves, endocardium, ganglia and nerves — is observed in the high mortality of cases that enter on a pneumonic toxemia with preexisting cardiac disease. We have all seen instance after instance of a patient making a bold fight to weather the storm, and experiencing sudden cardiac collapse, either in midstream or on the brink of convalescence. Only recently I witnessed an acute pneumonia in a young man of 22 years, an alcoholic, with myocardial degeneration and high-grade mitral stenosis and insufficiency, all sclerotic and probably syphilitic in origin. He went to bed in the beginning of an intense pneumococcus infection with a heart widely dilated, an irregular pulse and edematous extremities. Within two days he showed

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a steady, remarkable cardiac gain. The jugular pulses became almost undiscernible, the apical pulse regained its regularity, the edema entirely disappeared from the extremities. With these signs of cardiac rehabilitation, the whole aspect of the pneumonia (croupous or fibrinous, as shown at the necropsy) altered. The patient was no longer cyanotic, the breathing became more free, and it appeared almost as though even this desperate case might win out against the acute disease. Suddenly and coincidently with an apparent crisis, all the signs of cardiac distress reappeared, and in a brief period evident cardiac, not pulmonary, death supervened. The heart had reached its recuperative limit, and could draw no further on a reserve force, because it had no further stock in store. In the same manner a tobacco- or alcohol-weakened cardiac muscle may decide the issue between life and death in an otherwise favorable pneumonia.

CONCLUSION

Without attempting to minimize the influence of the vasomotor system in the causation of a high mortality in pneumonia, it would seem as though we ought not to be satisfied, on the basis of either clinical or laboratory experience, to regard the heart in any other way than as the factor of prime importance in the safety or danger of the great majority of asthenic pneumonia patients. More and more does the prevalent pneumonia seem to be tending away from the well-recognized, frank sthenic type, to the low-grade, asthenic, bronchocatarrhal forms. The more certainly this is true, the more inevitable will be the necessity of safeguarding the heart from start to finish, not so much by the use of drugs as by their avoidance (especially cardiodepressants like nitroglycerin and alcohol), not so largely by treatment as by the studious prevention of an overdose of solicitous care. Hygiene of the intestinal tract, sane feeding, the intelligent use of an abundance of clean air of the right temperature, and

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the insuring of ample periodic freedom from the doctor, nurse and family will go farther than any others toward supporting the organ whose staunch cooperation is essential to the happy outcome of the case.

1827 Spruce Street.

ABSTRACT OF DISCUSSION

Dr. James M. Anders, Philadelphia: I feel convinced that Dr. Willson is right in stating that pneumonia has been assuming an irregular bronchopneumonic type in recent years to a greater degree than formerly. This fact may be attributable to the more constant and general prevalence of various forms of influenza. The view that death in uncomplicated cases of pneumonia is due to the specific effect of the toxemia on the heart is widely accepted. Perhaps it would be more nearly correct, in the present state of our knowledge, to say that death is caused by the general rather than the local effect of the toxemia. As pointed out by Dr. Willson, the whole vasomotor system is profoundly involved in many cases. The heart is frequently dilated, especially the right side, and filled with firm coagula. It has long been held that if the more usual cardiac complications, such as acute endocarditis, pericarditis and fatty degeneration in protracted cases, be excluded, the changes presented by the myocardium are conspicuous by their absence. The results of the microscopic studies by Dr. Willson, therefore, are not a little surprising, but will constitute a distinct advance in our knowledge of pathologic changes found in the heart in pneumococcic infections, especially if confirmed by the findings of other competent observers. The frequency and seriousness of the disease in question make it desirable that further histologic investigations of the subject be undertaken. I quite agree that cold or fresh air in the treatment of pneumonia is one of the best, if not the best measure at our command, but it should not be indiscriminately employed. It has not a specific influence, but does increase resistance to the toxemia. Again, it should not be employed in cases in which active kidney lesions preexist.

Dr. William S. Thayer, Baltimore: Does Dr. Willson believe that the type of pneumonia has really changed from a sthenic to an irregular asthenic type? On what does he base his opinion? In over twenty-five years' observation of pneumonia in various regions I have not been able to detect any essential differences in the clinical character of the disease beyond, of course, the common variations in different epidemics. I am quite familiar with this assertion with regard not only to pneumonia but to other acute febrile diseases, especially typhoid fever. I rather think that the old-fash-

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ioned "typical case" is essentially a picture in the mind of the observer based on text-book descriptions—an impression so strong that in the course of years it becomes interpreted as actual experience; and that the common impression that such a disease as pneumonia is changing its type is largely based on the circumstance that in practice pneumonia shows frequent variations from this picture. I am not aware that such change in the clinical manifestations of the disease has occurred.

Dr. Robert N. Willson, Philadelphia: In answer to Dr. Thayer's question, I have two grounds for the assertion that the prevalent type of pneumonia is gradually changing from that of the old-fashioned book type of fibrinous or croupous pneumonia to the low-grade or bronchocatarrhal form. First, my own personal experience in a series of several hundred cases, both in hospital and private work, leads directly to such a conclusion. This experience covers and includes considerable necropsy and microscopic work in confirmation of the diagnoses. My second basis of argument is the result of not a few conferences held with men in various localities over the country, who agree with me in my conviction as the result of their experience and study. Dr. Anders' statement, made a few moments ago, in discussing my paper, furnishes a case directly in point. I had not previously heard his position in the matter. I shall welcome similar studies of the heart in the pneumonias as confirmatory of my own. In every instance of pneumonia widespread damage to the cardiac musculature will be found. When this fact is recognized I think we will begin again to regard the heart as the organ and force mainly to be safeguarded and conserved, and to lay a little less stress on the vasomotor factors in grave cases of pneumonia.

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THE TREATMENT OF HEART INVOLVEMENT IN SYPHILIS

BASED ON A STUDY OF 300 CASES*

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AND

JOHN CARROLL, M.D.

NEW YORK

We have already written concerning the great frequency of heart involvement in syphilis.[1] Here and elsewhere,[2] we have discussed the character of the changes in the organ, pointing out that the most frequent and important lesion in all stages of the disease is one of the heart-muscle which is dependent on a periarteritis of the coronary vessels. This lesion was apparently first described by Isaac Adler,[3] and its frequency of occurrence, since noted by many, has been recently verified by Warthin,[4] who has demonstrated with considerable constancy the presence of spirochetes in these characteristic foci.

In another paper,[5] presented as a continuation of our study of this subject we have discussed the symptoms and diagnosis of the complication.

Some of these cases have now remained sufficiently long under observation to permit us to discuss with some authority the question of treatment and its results, covering cases in the secondary and tertiary

* From the Second Medical Service of the City Hospital.

1. Brooks, Harlow: A Study of the Heart in Syphilis, Med. Rec., New York, 1912, lxxxi, 351.
2. Brooks, Harlow: Clinical Observations Concerning the Heart in Syphilis, Inter-State Med. Jour., 1913, xx, No. 6; The Heart in Syphilis, Am. Jour. Med. Sc., 1913, cxlvi, 513.
3. Adler, Isaac: Observations on Cardiac Syphilis, Tr. Assn. Am. Phys., May 3, 1898.
4. Warthin, A. S.: Tr. Assn. Am. Phys., May 13, 1914.
5. Brooks, Harlow, and Carroll, John: The Symptoms and Diagnosis of Involvement of the Heart in Syphilis, Based on a Study of Two Hundred Cases, New York State Jour. Med., 1913, xiii, 328.

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stages of the disease. It is our purpose to present in this paper certain aspects of this important side of the subject in so far as our rather brief though active experience now goes.

We have found it very difficult to discuss treatment in an analytical way inasmuch as so many cases have come under our observation on our hospital services, where definite data could not be elicited as to the precise methods of specific treatment previously employed, nor of its extent.

Obviously in a large percentage of the cases the time at which the heart-lesion developed could not be ascertained; in fact, this point could be surely fixed only in some of the secondary cases. The character and extent of previous treatment for circulatory discrepancies can also not be definitely determined.

We have included in our list for analysis a number of cases which have been treated in various hospitals or by private physicians with entire disregard of the luetic origin of the cardiac fault. Such instances have been included because we have found that comparison of these with those treated on the assumption of a definitely syphilitic change affords a basis for conclusions of value. Only four instances are found, however, in this series in which improvement without specific treatment took place.

Since a considerable number of cases have only been conclusively recognized by lesions discovered post mortem, it must be understood that it is highly probable that the percentage of fatal results in this group of three hundred cases is overestimated, and it is therefore not mentioned, as having no accurate bearing on the treatment of this complication. The apparent recovery or signal benefit of equally desperate cases, when treated on the basis of the luetic origin of the heart defect, certainly indicates the necessity of such a therapeutic basis. We are keenly aware that so crude an analysis as is possible on a material of this character does not establish a certain scientific fact,

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but we feel that our study, covering as it does over three hundred cases, has led us to conclusions of very real applicable value from a clinical standpoint.

It will be noted throughout that our methods of treatment vary greatly, and that no one routine type of drug or procedure has been adhered to. This may be in part due to the fact that our therapeutic studies have been, and still are, in an experimental stage, but chiefly because we have been driven to the conclusion that in the treatment of patients suffering from this complication each instance must be definitely individualized, and that no one routine method will be found to apply with equal benefit in all cases. Unscientific as this conclusion may appear to some, to those long actively concerned in the treatment of disease in routine patients, it needs no defense, and the absolute necessity of such a basis for the best therapeutic results will be apparent.

We again wish to emphasize the fact that the essential lesion, in so far as the heart in syphilis is concerned, is a periarterial granulomatous or inflammatory change affecting the heart-muscle. From the standpoint of treatment, we believe that this assumption is most important, for our studies have shown the final or immediately lethal lesion in most cases to be a giving way of the muscle. Furthermore, we are convinced that in most cases where improvement has followed treatment it has been accomplished by a clearing up of these rather than of other lesions, though we recognize with Sachs, Collins and many others after them that a true endocarditis, even of considerable standing, may be absolutely removed by specific treatment.

We also wish to state that in our opinion some of the most brilliant results attributed to specific treatment in cases of syphilitic aortitis have in reality been achieved from improvement of the universal heart-muscle lesions, for many of the symptoms commonly attributed to this lesion are really due to muscle dis-

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ease. This assumption is apparently supported by the recent pessimistic but undoubtedly accurate studies of Warthin.

CASE 1 (231).—M. F., woman, aged 50. Negative history as to lues. Five years ago, epigastric and precordial pain with vomiting, dizziness, headache and weakness. Shortly after, dyspnea on least exertion. One year later edema, precordial pain reflected down left arm into hand. All symptoms recently greatly increased. Physical examination showed poor muscle tone with systolic at mitral and at aortic rings. Broad area of retrosternal dulness, tenderness over manubrium. Roentgenoscopy shows dilated arch. Under circulatory treatment in hospital for three months, constantly losing ground, all symptoms progressing. Wassermann reaction negative. One grain mercuric salicylate given intramuscularly with idea of activating Wassermann. Marked improvement in pain within twenty-four hours. Circulatory drugs discontinued and mercuric salicylate continued in vigorous dosage. Patient now up and about ward, apparently free from all symptoms except on exertion. Wassermann reaction positive. Roentgenoscopy shows no apparent change in aortic shadow.

TREATMENT IN SECONDARY CASES

The early cases treated have mostly occurred either in the private practice of one of us (Carroll), or in the service of our colleague, Dr. J. A. Fordyce, who has greatly encouraged our studies of this subject. Twenty-four such instances have been observed. Two fatalities occurred among them (previously reported) but in both the nature of the disease and its complication had not been recognized in sufficient time to admit of proper treatment. Confirmatory necropsies were secured in both. Apparently complete recovery without any subsequent heart defect took place in all the other cases, save one to be mentioned later. We wish in this regard to point out the care which should be exercised by those in charge of early syphilis that cardiac strain be avoided until treatment has been established, and that the same necessity for consideration of the circulatory apparatus be recognized as in the other infections, diphtheria, rheumatism, septicemia and the like.

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CASE 2 (199).—Man, aged 34. Service of Dr. J. A. Fordyce. In secondary stage of the disease. Complains of shortness of breath, sudden attacks of precordial pain. Chills, fever, leukocytosis and the physical signs of pericarditis. Complete disappearance of signs and symptoms within three days after two doses of neosalvarsan (intravenously). The cardiac signs appeared within four weeks after initial lesion, which in this case was on nose. Apparent cure followed. Subsequent combined treatment.

Although practically all the early cases under our observation have been treated by the more modern methods, that is, with salvarsan, we are convinced that vigorous treatment with mercury in this stage would probably also result in almost as brilliant results. We wish to assert that, aside from general prophylactic measures, the treatment of cardiac invasion in early syphilis should be directed only to the specific infection and that circulatory treatment *per se* is at this time unnecessary and probably unwise.

Although we are convinced that in by far the greater majority of cases of early lues cure of a cardiac complication may be confidently expected, certain exceptions exist. This has been well illustrated by a case referred to one of us by Dr. Alphonse Wren.

CASE 3.—Patient, woman of 25. Came under observation in the aggressive secondary stage of the disease. She had been treated, apparently mostly with mercury and the iodids in various dispensaries and by private physicians. In spite of treatment exhibits mucous patches, marked skin rash, periosteal tenderness, fever, falling hair and other evidences of active secondary lues. While still under vigorous treatment with mercuric chlorid internal, mercurial inunctions, and after three doses of salvarsan carefully administered in an excellent clinic, developed cardiac muscle insufficiency, dilatation, active aortitis (without aneurysm) endocarditis and edema and cyanosis with severe dyspnea. Salvarsan intravenous again repeated in maximum dose. Mercuric salicylate injected intramuscularly until marked salivation and other evidence of mercurial poisoning appeared. Digitalis, strophanthus, camphor and the usual cardiac regimen apparently produced no effect whatever. The case was progressing rapidly and absolutely unchecked by either specific or circulatory measures when she passed out of our observation. Though her subsequent history cannot be ascertained, it is impossible to assume other than that early death followed.

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In so far as could be judged by study and observation of this case, treatment of all kinds was entirely without avail in so far as checking the course of the infection or relieving the heart complication was concerned. This has been the only case in our observation in which treatment in the secondary stage has been apparently useless. Inquiry among syphilographers of wide experience has brought to light other and probably similar cases. They would, however, appear to be quite unusual.

TREATMENT IN LATE CASES

Most of the cases comprised in this series are those occurring, or at least presenting themselves, on an internal service for treatment in the tertiary or late stages of the disease; 277 instances of this type are included.

A few patients appeared for treatment for the first time because of their cardiac condition; but in most instances, and in practically all cases which came to our hospital service, they had been for a greater or lesser time under treatment either by private physicians or in institutions for their circulatory discrepancies. While in some of these cases a certain amount of benefit had been derived from such measures, mostly applied entirely without recognition of the cause of the circulatory defect, the very fact that they appeared for treatment shows that these measures in themselves had been found inadequate, probably even at the very outset of the complication. As illustrative of this point we wish to present briefly the case of a fire captain 52 years of age.

CASE 4.—He came to one of us suffering severe precordial pain and so marked a grade of dyspnea that he was hardly able to get about. He had been ordered before the retiring board because of physical disability. On examination he showed loud, double aortic murmurs, and irregular and considerably dilated heart, together with the symptoms of a probable aortitis. The man gave a history of a probable rheumatic fever but denied that of syphilis. He was placed

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on digitalis, but without good effect. Because of the failure to respond, and also because of the evidence of an old tibial periostitis, although a Wassermann had been refused, he was taken off the cardiac medication though, of course, circulatory precautions were still insisted on. He was tentatively placed on protoiodid of mercury by mouth. Within a few days such marked improvement had taken place that when the patient was confronted with the facts of the case he admitted a syphilis twenty years ago, which had been at that time briefly treated. A continuation of the same line of treatment with the protoiodid of mercury, assisted by potassium iodid, has resulted in complete disappearance of the dyspnea and other evidences of cardiac incompetence. The double aortic murmurs have practically disappeared and he has been doing full duty for some twelve months and is to-day in comparatively complete health, although still under treatment with the mercury.

These two facts stand out in this illustrative case: circulatory medication was entirely without avail, complete circulatory relief was afforded by the simple administration of mercury.

Notwithstanding frequent brilliant results of this kind, in tertiary instances we have found it by all odds most advisable to also place the patient under the usual hygienic and therapeutic regimen indicated by the circulatory condition. Those cases which, independent of the cause, should be put at rest or in bed, should be, of course, so managed. Furthermore, when digitalis, strophanthus, camphor, strychnin or epinephrin seem to be indicated, they should be given. We have found, however, that in most instances these measures do not give the expected amount of improvement, except for that directly due to rest, in whichever form it may be decided, unless and until the patient has been under the effects of specific medication of one or another variety. Not at all infrequently, as in the instance cited above, such a measure is at once followed by so marked benefit that the drug measures designed for circulatory compensation may be advantageously discontinued. In long-standing cases, however, particularly those in which it may be fairly assumed that fibrosis has taken place in the heart-

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muscle, the use of digitalis and its adjuvants or substitutes is absolutely necessary. A fact most vividly shown, however, is that these drugs used alone fail in most instances to give good results unless combined with the specific methods.

Although immediate improvement may follow the introduction of specific medication, it has been amply demonstrated in this, as in all other types of luetic disease, that for permanent results or even for steady progress, the specific medication must be persistently carried out. With a discontinuation, such as has taken place frequently when patients insist that they are sufficiently well to leave the hospital, and probably rarely then continue to carry on the treatment in anything like an adequate manner, relapses are apparently almost certain to occur. We have noted that when the treatment has been thus interrupted when it is resumed rarely indeed does a prompt response to it occur comparable to that first manifested. In other words, a tolerance of the lesion against the drug seems to have become established in some cases.

Case 5 (67).—Man, aged 51. Chancre at 30 years. Local treatment only. Present illness began in 1908. Chief complaint, dull, boring pain in left chest associated with dyspnea. For two years a constant increase in distress. Has been under almost constant circulatory treatment without relief. Wassermann positive. Given 1 grain mercuric salicylate hypodermically every 5 days. Pain dyspnea and edema began promptly to subside. Treatment continued for nine months (sixty-six injections); three doses of salvarsan also given intravenously together with various symptomatic measures. Patient able to be discharged and to resume work as cook after three years of total invalidism. Two months later, treatment having been discontinued, symptoms reappeared, to disappear promptly under resumption of the mercury. The subsequent history has been a return of symptoms whenever specific treatment has been discontinued. Circulatory measures are now necessary to reach the results previously easily obtained by purely specific drugs.

Where the patient can be closely followed and treatment persistently enforced, progress seems to be steady to the point of apparent cure in no inconsider-

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able number of cases, as indicated by the fact that of the series of 300 cases so treated 116 have shown apparently permanent benefit if not actual cure. The most impressive fact of all is that a large number of cases which appear apparently hopeless go on to clinical cure.

TREATMENT WITH MERCURY

As to the precise method of specific treatment which meets with best success in these complications of syphilis, no conclusion appears as yet possible to us except that, at least in most instances, it is a matter of individualization. In not a few cases best results seem to follow an initial vigorous administration of mercuric salicylate given intramuscularly, and in general this would appear to us to be on the whole the most desirable method at the outset. The drug should be pushed to its full point of toleration, but may be subsequently replaced by mercury in the form of the protoiodid or bichlorid introduced by mouth. In some cases, as in an instance already cited, the protoiodid appears to be very desirable. It seems to us that such instances are those which do not manifest the most aggressive and active symptoms and, though we are well aware that this form of mercury does not enjoy a good repute with syphilographers in general, it has given us excellent results in many of these heart cases.

Mercuric chlorid has also given us good effects in some instances, either given by mouth or by hypodermic administration.

CASE 6.—J. D. Seen seven years ago with Dr. C. J. Imperatori. Patient a powerful, rather obese man, aged 26. Patient unconscious, complete anuria, heart enormously enlarged. History of long standing, apparently progressive double aortic lesion with very unsatisfactory response to digitalis, etc. Apparently *in extremis*. He had denied lues, but because of social evidence to the contrary he was given vigorous dosage with mercuric chlorid by mouth and inunctions over precordium of blue ointment. Within a few hours return of renal activity and consciousness, with subsequent cessation of precordial pain and reappearance of regular, full pulse with

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marked double aortic murmurs and strong, vigorous muscle contractions. Mercury continued with occasional digitalis, which now acted in a proper manner. Given potassium iodid with continued benefit. He largely disappeared from observation up to last year, when he returned with a history and condition of relapse which had developed apparently from discontinuance of treatment and from moderate dissipation. He had meanwhile carried on his work and lived an ordinary life. Relief again followed resumption of treatment but he suddenly died some four months later, apparently from acute dilatation after intercourse.

Inunctions of mercury ointment given in the usual courses also seem to act very well in many cases. In one notable instance we found little result and a very poor toleration of mercury until the old-fashioned, and to our mind usually uncertain, treatment with vapors of calomel was instituted. In practically all instances we have received best results when the form of treatment or of the drug was from time to time altered but, on the other hand, actual interruption of treatment inside of two years for no more than a few months has been followed frequently by relapse and a subsequent unsatisfactory response to this drug. We are anxious none the less not to give the impression that we believe that every case of late syphilis with heart complications will respond to mercurial treatment, and to emphasize this point we cite the following case:

Case 7.—V. H., man, aged 51. An irregular, though shrewd, practitioner in venereal diseases. Lues contracted twenty years ago. Was very aggressively treated at that time with inunctions and by "mixed treatment." Apparent cure. Subsequent life often dissipated. Late in 1913 began to be troubled by anginal attacks, dyspnea, cyanosis and spontaneous attacks of dizziness. Wassermann reaction found to be positive. Diagnosis of luetic myocarditis, adhesive pericarditis, aortitis. Varied mercurial treatment promptly and vigorously resumed, associated with occasional use of iodids. After this some, though unsatisfactory, response to digitalis, strophanthus and epinephrin, all of which had been previously found inert. Wassermann became negative. Patient absolutely refused to permit the use of salvarsan, saying that he preferred to die rather than to submit to it. Soon died, with the ultimate typical picture of a myocardial degeneration.

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TREATMENT WITH SALVARSAN

Salvarsan has been employed in the treatment of seventy-five of this series. In the acute or secondary stage, used independently of mercury, it has in nearly every instance been followed by immediate improvement of the compromised circulatory mechanism, even in patients in whom the circulatory defect appeared to be serious. In such cases it may be that complete cure *might* follow the use of this drug alone. In all, however, a follow-up course of mercury has been prescribed; some instances observed by us, but not included in this analysis in which salvarsan alone has been employed have not yet remained a sufficient time under observation to allow us to judge as to the permanence of such apparent cures. These brilliant results are much less frequently apparent in later cases, however, and such is our confidence in and reliance on mercury that in no cases have we ourselves continued the use of salvarsan alone.

Our experience has indicated to us that, while no doubt salvarsan gives a most prompt response, its permanency in tertiary complications, referring entirely now to those of the heart, does not appear to be established unless the treatment is followed up by the protracted use of mercury. Where very prompt response to treatment seems to be necessary salvarsan is given, but in cardiac even more than in other complications of this infection a very serious degree of reaction may follow the giving of salvarsan and more than seldom we have been greatly alarmed by circulatory collapse which has followed the administration of salvarsan in those cases especially in which symptoms and signs indicated particularly aggressive invasion of the heart-muscle.

We have been impressed with the observation that those cases which showed disturbances of rhythm as a result of the myocardial invasion are most likely to exhibit serious reaction after the use of salvarsan. We have therefore esteemed it to be good practice to begin

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the use of arsenic in these cases of heart complication by small doses, allowing the subsequent ones to be larger if no serious grade of reaction is excited. Of all the cases treated by us there were none in which any grave circulatory disturbance threatened as an apparent result of a maximum initial dose of mercury.

As a natural result of these observations we have in questionable cases, and when time did not seem to be of paramount importance, usually first placed the patient on mercury, giving the salvarsan later. We are of the impression that best results are often reached when the salvarsan injections are widely spaced in the course of routine mercury administration. The later injections of salvarsan are much less likely to give serious disturbance than the earlier, especially the first one. Of course it goes without saying that salvarsan is administered only as intravenous injections. It is a very difficult matter to judge, nor do we feel that our cases have been sufficiently numerous to permit of definite conclusions, but we are of the opinion that the old salvarsan is more efficacious in the relief of heart complications in syphilis than neosalvarsan. We have not been able to see that the newer form of the drug produces any less serious collapse than the old in those cases in which this incident arises.

THE IODIDS

We have extensively employed the iodids, mostly potassium iodid, in the treatment of these cases of heart invasion. In no instance, however, have we been able to convince ourselves that it acts in any way as a specific. Nor does it, according to our observation, check the progress in an aggressive case. For illustration, we have not found in cases of circulatory deficiency when drugs of the digitalis group failed to act, that results were obtained by combining the administration of the iodid. This, as we have already stated, is to be fully expected, especially in previously untreated cases both with mercury and salvarsan. We

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have not, however, tried out the iodids alone in cases of secondary syphilis in which heart involvement was present; hence, perhaps, we are not justified in definite conclusions, but we do not believe that this drug is to be considered as a specific in the treatment of active lues.

In tertiary cases, however, there is no doubt whatever in our mind but that the iodids materially assist in the clearing up of the infiltration and exudates, and their effect on gummatous tissue is too well established to admit of question. The point which we wish to make is that, while it is most useful in the absorptive stages of treatment, it does not act as a true specific. Iodin should be used after the case has been thoroughly mercurialized, or after salvarsan has been liberally given, and not before or during the early exhibition of these drugs.

THE EFFECT OF TREATMENT

That great clinical improvement takes place in most cases and a certain degree of benefit, though perhaps temporary, in practically all, is the most gratifying fact shown by this study. We are entirely convinced that as definite and brilliant results follow proper treatment in cardiac syphilis as in gumma of the brain, in syphilis of the bones or even in the local lesions of the skin and mucous membranes in the same stages of the disease. As to the question of permanence, we are not so certain, comparatively. This is quite as must be expected from the crucial nature of the organ and the very limited degree of restitution and compensatory hyperplasia of a functional type which may take place in lesions of the heart-muscle.

In regard to the manner in which the curative drugs act, we have but little absolute anatomic evidence, for in but two patients who died after what we have considered adequate treatment have necropsies been secured. Sections of the heart-tissue in these two cases (one reported[6]) showed a total absence of the

6. Brooks, Harlow: Am. Jour. Med. Sc., 1913, cxlvi, 513.

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characteristic perivascular cell hyperplasia and infiltration, or of active arteritis in the walls of the coronary vessels. In both instances, however, insulae of fibrosis were found isolated and perivascular in position which still showed evidence of fibrous hyperplasia, just as in simple fibrosis, but in neither were any lesions present which could be justly spoken of as luetic. In neither instance were we able to demonstrate spirochetae. In view of the report of Warthin already mentioned, however, we are not prepared to say that they might not have been present and our failure to demonstrate them may have been due to technical deficiencies; we can only say that anatomically, as clinically, all evidences of active syphilitic disease was wanting, although the scars or results of course remained.

In incompletely treated cases which came to necropsy we have without exception been able to demonstrate active lesions of a quite characteristic and unmistakable type.

In common with most who have recently studied large groups of any type of syphilitic idsease we have not infrequently seen cases in which apparent clinical cure had taken place and yet in which a positive Wassermann reaction could be secured after a sufficient period of interruption of treatment had elapsed. We have looked on these instances as examples of probably cured syphilis in which a persistent Wassermann still remained. This opinion has been already expressed by us in a former paper.[7]

We have had abundant evidence of the fact that the fibrosis which follows on or occurs with the hyperplastic and degenerative alterations of the heart in syphilis are not removed by treatment; further, we are of the opinion, difficult to entirely prove, that this fibrosis may continue to progress even after the primary etiologic factor may have been entirely eliminated. Such is the general trend in fibrosis of non-

7. Brooks, Harlow: Clinical Observations Concerning the Heart in Syphilis, Interstate Med. Jour., 1913, xx, No. 6.

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specific nature, and we are inclined to account on this basis for those cases which, while greatly improved or arrested by the treatment, still, in so far as cardiac fibrosis is concerned, continue to progress just as in those cases in which the lesion may have been excited by a rheumatism, a nephritis or the like. There is then a large group of cases in which definite limitation of actual cure is present.

THE LIMITATIONS OF TREATMENT

We are of the opinion that the limit of benefit for specific treatment in these conditions is commonly reached in tertiary or late cases, when the activity of the actual syphilitic process has been checked or cured and when thereafter by the use of the iodids a maximum degree of absorption and tissue restitution has followed, and when on top of this a maximum effect has been produced by the various drugs and methods designed for circulatory improvement.

Some such cases probably demand the occasional administration of mercury or arsenic. We have been unable in several such instances, however, to go beyond a certain point in beneficial treatment, and when in these the circulatory drugs begin to fail us, the downward progress is, in our observation, rapid, nor is it to be checked by any form of medication, specific or otherwise. The patients then assume precisely the same position as late cases of myocardial degeneration or fibrous substitution, such as may develop in the course of many other diseases. At post-mortem these instances commonly show extensive patches of myofibrosis, or advanced disease of the coronary arteries with consequent muscle ischemia.

From our somewhat limited experience with cases of acute secondary syphilitic involvement of the heart, we are of the opinion that no limitation of result exists short of true cure except in those rare cases, similar to the one cited, in which specific drugs are entirely powerless. We are of the idea, it is true from a

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clinical basis only, that complete and absolute cure is to be expected in this stage of the complication.

WHEN SHOULD SPECIFIC TREATMENT BE ENTIRELY DISCONTINUED?

The answer to this question is most difficult. Obviously in some instances it must be continued after a negative Wassermann has been obtained; for we frequently find patients in whom activity is evident and yet who give a negative Wassermann. We have also noted above that we occasionally find patients still presenting a positive reaction who otherwise appear to be cured.

From our experience in the treatment of syphilis in other departments of medicine, as well as in circulatory involvement, it is obvious that medication of a specific character must be continued for a considerable time, at least one year, after all signs of activity have subsided. We believe, however, that better results are obtained by periodic rather than continuous medication in the final stages and also by variation of the type of the drug or in its form of administration.

We think that treatment should be continued just so long or longer as it is apparent that benefit is being reached either by the specific drug or by the adjuvant employment of a circulatory stimulant. We further believe from our clinical observation, and from our own as well as the recent anatomic studies of the heart-muscle in syphilis by Warthin, that antispecifics should be from time to time given throughout lifetime in certain cases. It is obvious that just so long as any evidence whatever of luetic activity in any part of the body is manifest, treatment should be vigorously pushed, though periods of interruption may be elected so that disease resistance toward the drugs falls off.

THE SUBSEQUENT MANAGEMENT OF THE CASE

We have just pointed out that, except in acute secondary involvement, we feel that antiluetic drugs may be occasionally beneficially exhibited throughout

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life even though they may not perhaps be directly indicated by the immediate appearance of the case itself. Aside from this, the subsequent management of the case should be essentially along circulatory lines and it should be carried out with the fact well borne in mind that practically certainly there are foci of fibrosis in the heart-walls, changes in the endocardium and in the walls of the coronary vessels which are in all probability irremediable and permanent.

This recognition appears particularly important in the determination of the proper hygienic management of the case, especially in regard to selection of occupation or sports and in the limitation of such habits as that of smoking. In late cases it can certainly never be assumed that we are dealing with a perfectly normal heart no matter how complete the cure may seem to be. While we make this statement, based on our considerable necropsy experience with these cases, from clinical observation alone one might well assume that complete cure even in some late and advanced cases had taken place. We do not feel, however, that any of these apparent cures have yet remained a sufficient number of years under observation to overthrow the lessons of pathologic anatomy.

THE PROGNOSIS

In acute cases, and in the secondary stage particularly, we believe that except in those instances in which resistance to the specific drugs is shown, a good prognosis as to cure may be given.

In cases in which incomplete or brief specific treatment only has been given, we believe that almost without exception great improvement may confidently be promised even in many instances in which circulatory measures alone show little benefit. When, after the patient has been thoroughly placed under the effects of the specific medication, the circulatory drugs still fail to act, the prognosis as to cure or further improvement is definitely bad.

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Nevertheless, a bad prognosis as to relief or a considerable period of reasonable comfort and usefulness is never justified until the combined treatment has been thoroughly tried out. No more gratifying results are reached in chronic cases of any disease than are often shown in cases of this type, apparently at first thought altogether hopeless.

The prognosis in cases which have relapsed after marked or reasonable improvement is not good. Disturbances of rhythm particularly which have failed to show early and definite improvement under treatment rarely justify a good prognosis.

CONCLUSIONS

1. Cases of heart involvement in early syphilis may be fully cured irrespective of the character of the lesion by vigorous specific treatment alone and independent of circulatory measures.

2. Even well-established and late cases usually respond to treatment with cure, or marked though perhaps temporary benefit.

3. In most tertiary instances purely circulatory measures produce but slight benefit unless preceded by or combined with specific medication.

4. Interrupted or inefficient treatment establishes an immunity or resistance on the part of the lesions against the specific drugs employed. Hence the importance of vigorous and carefully systematized treatment.

5. The most satisfactory treatment is one which combines the use of salvarsan with mercury and the iodids. Combined treatment *may be* unnecessary in early cases but it is essential in late ones.

6. Salvarsan, preferably old salvarsan, produces in most instances the quicker results. It is capable, however, of inducing serious symptoms and in untried cases of heart involvement it should be administered in small doses until its action has been ascertained,

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particularly in those lesions characterized by disturbances of rhythm.

7. Mercury alone may produce apparent cure. Best effects are secured with this drug when its form is from time to time changed. Its use appears to be indispensable in all well-established cases.

8. The iodids are valuable adjuvants in the treatment of these cases, especially in their late stages, but they are apparently without specific action.

9. Permanent injury to the heart must be assumed to have taken place in late cases, even though prompt response to treatment and apparent cure occurs.

10. Successful treatment rests primarily on the recognition of the *cause of the disease* and on its specific treatment.

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THE FOUR COMMON TYPES OF HEART-DISEASE

AN ANALYSIS OF SIX HUNDRED CASES

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To classify cases of disease according to their pathogenic agent or process, and not solely by naming the region affected or the function disturbed, is the ideal of scientific progress in medicine.

But until the last decade we have made little advance in this direction as regards the diseases which gravely disturb heart function. Thus we still find in standard text-books a section devoted to "mitral regurgitation," its diagnosis, prognosis and treatment, although mitral regurgitation is almost as vague a phrase as "spinal paralysis" or "brain fever." Just as a "spinal paralysis" may be due to trauma, to the tubercle bacillus, to the *Spirochaeta pallida,* to the organism of poliomyelitis or to cancer, so "mitral regurgitation" is only a symptom caused by the action of streptococci, by the degenerative lesions of arteriosclerosis, by the muscle-tiring resistance of nephritic hypertension and probably by many other causes. It probably contributes its mite to the downfall of cases of pernicious anemia, typhoid fever and puerperal sepsis. Hence there can be no rational prognosis or treatment of mitral regurgitation but only of the various underlying diseases in which this leak is a symptom.

A similar criticism applies to all diagnoses of "myocarditis." The micro-organism of rheumatism and of syphilis, the ravages of arterial disease and perhaps many other causes may produce the lesions of chronic fibrous myocarditis, with or without recognizable symptoms. A diagnosis of myocarditis is like a diag-

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nosis of "ulcer"; it calls for an etiologic qualification, such as syphilitic or tuberculous.

The matter has many practical aspects. A sane prognosis and treatment of "aortic regurgitation," for example, depends on knowing or guessing what disease has produced it. Even physical diagnosis may have to await an intelligent interpretation of its results until we make up our minds what micro-organism is at work, in the heart, as well as elsewhere in the body. When we hear a low, rumbling presystolic murmur at the heart's apex and an early high-pitched diastolic

CLASSIFICATION OF CASES WITH FAILING HEART

	Male	Female	Total
1. Rheumatic	108	170	278
2. Syphilitic	52	22	74
3. Arteriosclerotic	53	40	93
4. Nephritic	59	58	117
	272	290	562 (93% of all)
Goiter heart	3	5	8
Doubtful cases	19	11	30
	294	306	38 (7% of all)
Total			600

along the left sternal margin, our conclusions about the mitral valve depend on our answer to the question, "Is syphilis or 'rheumatism' at work here?" If the former, then the mitral valve is probably sound; if the latter, probably diseased.

Four relatively new tests have now made it possible —as I think—to reclassify cardiac lesions more satisfactorily: the Wassermann reaction, the "red test"[1] of renal function, the measurement of blood-pressure and the roentgenography of the chest. When auscultation, percussion and the older methods of urinary examination leave us in the lurch, the four diagnostic methods just mentioned can often guide us aright.

With the help of these methods I have attempted a classification of 600 recent hospital cases in which a

1. Phenolsulphonephthalein.

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failing heart was the most notable feature. The results are shown in the accompanying table.

THE RHEUMATIC TYPE

Under "rheumatic" are grouped the cases of weakened heart, adherent pericardium and valvular disease associated with (*a*) acute non-gonorrheal polyarthritis ("rheumatic fever"); (*b*) chorea (of Sydenham's type); (*c*) acute tonsillitis, and (d) "primary endocarditis" with negative Wassermann reaction, especially when the cardiac symptoms followed these diseases during the patient's youth. In my opinion it has been demonstrated by the converging results of English, German and American work as the best working hypothesis that a streptococcus is the exciting agent of acute "rheumatism," chorea, endocarditis and tonsillitis.[2] This streptococcus in the joints produces acute rheumatism, in the brain chorea, in the heart endocarditis, myocarditis and pericarditis. It may attack the heart first and later the joints. Then our old terminology would make it appear that endocarditis is the "cause" of rheumatism. It may attack first the brain and heart, appearing later in the tonsillar or peritonsillar tissue. It may attack the heart and kidney simultaneously, so that we find true cardiac and renal disease from an identical organism, as Libman and others have maintained.

This form of streptococcosis is essentially a disease of youth, both in man and in the animal experiments of Rosenow. In 60 per cent. of the cases here analyzed the disease began (usually in the joints) before the twenty-second year. The patient rarely dies a mechanical or heart-death, usually an infectious death, by terminal, progressive or relapsing infection. Women are affected more often than men—nearly twice as often in these statistics.

The mitral valve, the pericardium and the myocardium are the favorite seats of bacterial invasion, the

2. As well as certain cases of pleuritis, pericarditis, peritonitis, iritis, meningitis, pneumonia and nephritis.

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other valves much less often. In the valves this form of streptococcosis produces usually stenosis with more or less leakage—but almost never leakage alone. In other words, mitral stenosis is *the* rheumatic (or streptococcic) valve lesion, although it is combined with aortic stenosis in a relatively small percentage of cases. It rarely produces aortic stenosis without a severer stenotic lesion of the mitral. It seldom if ever produces severe symptoms or death by leakage (mitral, aortic or both) alone, though it often produces systolic apical murmurs alone.

On the other hand, it seems probable that stenosis at the mitral or aortic valves involves regurgitation as well in practically every case.

When a cardiac streptococcosis occurs in its most virulent and intractable forms, we call it "malignant," "ulcerative," "septic" or "slow" (endocarditis lenta) and we find in the blood (according to Rosenow) a streptococcus culturally distinguishable from the organism of the milder cases. Nevertheless, I have here included all such cases in the "rheumatic" group of my table.

If the patient survives the second decade of life his smouldering, often recrudescent, cardiac infection may die out, leaving a serviceable heart, despite some narrowing at mitral or even at the mitral and aortic valves. Such cases carry a good prognosis and are often compatible with twenty, thirty or forty years of hard work.

SYPHILITIC HEART-DISEASE

Most cases of "causeless" aortic regurgitation appearing in men between 20 and 40 without "rheumatic" history have a positive Wassermann reaction and may be considered due to syphilitic aortitis with or without aneurysm. In negroes and south Italians we find a great deal of this type of heart-disease because of the prevalence of syphilis among them.

I have included twenty-four such cases, together with the eighteen aneurysms, among the syphilitic

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group in my table. To these I have added a group of thirty-two failing hearts, with or without evidence of valve lesions, without rheumatic history, without evidence of nephritis or arteriosclerosis, but with a positive Wassermann reaction. The permeation of the congenital syphilitic's myocardium with spirochetes (as shown by Warthin and others) makes it probable that in adults as well, many cases of myocarditis are due to syphilis. Probably a more searching study would result in transferring some cases from the arteriosclerotic to the syphilitic column in my table.

ARTERIOSCLEROTIC HEART-DISEASE

Under "arteriosclerotic" are included the cases of weakened heart in elderly persons with sclerotic peripheral arteries and hypertension, often with angina pectoris, occasionally with cerebral or peripheral symptoms of the arteriosclerotic type, and always with negative Wassermann reactions. I do not attempt to decide the question whether any of the hearts of this group are weakened solely as a result of renal arteriosclerosis or whether generalized arteriosclerosis works part or all the mischief. In either case arterial disease is the cause. If anemia is present these cases more often belong in the next group.

With further knowledge this arteriosclerotic group could probably be subdivided into the plumbic cases, those of infectious origin, etc. The heart itself shows enlargement, weakness, often arhythmia or gallop-rhythm. Angina pectoris and the cerebral and peripheral evidences of arteriosclerosis are often present. Such patients often live many years in comparative comfort. On the other hand, they may die suddenly of coronary stenosis or cerebral hemorrhage.

NEPHRITIC (OR NEPHROGENIC) HEART-DISEASE

Volhard and some other modern authors would designate many of my "arteriosclerotic" cases as benign "chronic nephritis." But it seems to me more

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convenient to confine the term "nephritic or nephrogenic heart-disease" to the cases of weakened and enlarged heart apparently resulting from the hypertension of glomerulonephritis.

Such cases are associated with urinary anomalies more marked than those seen in the arteriosclerotic group. The hyposthenuria, the nocturia, albuminuria, cylindruria and especially the functional weakness with the "red test" are very marked. The response to cardiac stimulants and to drugs like theobromin sodium salicylate is feeble. Demonstrable arteriosclerosis of the peripheral vessels is slight or absent. Uremic manifestations, retinitis and anemia are relatively common. The patients of this group average 36 years of age, those of the arteriosclerotic group 59 years of age.

Cases with positive Wassermann reaction or marked history of rheumatism are excluded. The heart itself shows enlargement, an accentuated aortic second sound, sometimes a systolic murmur at the apex or base, often gallop-rhythm and valvular first sound, occasionally an absolute arhythmia. The usual prognosis is for not more than one or two years of life.

Most of the cases of "senile heart," "cardiorenal" disease, "myocarditis" and myocardial weakness have been grouped with the arteriosclerotic cases, some with the nephritic, a few with the syphilitic.

The table shows that 93 per cent. of 600 successive and unselected cases of failing heart can be pushed into one of these four groups. How much violence was used in the grouping process I shall try to suggest later on.

THE EXCLUSIONS

Outside these four groups fall: (*a*) the "goiter hearts," that is, those showing no cause for weakness except a thyreogenic intoxication (exophthalmic goiter); (*b*) the "obese hearts," manifesting decompensation in very fat persons without streptococcic (rheumatic) or syphilitic infection, or arteriosclerosis, nephritis or thyreotoxicosis; (*c*) certain cases of myo-

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cardial weakness without any known cause. Had any of these occurred in athletes or ex-athletes they might have been called "athletes' heart." But they did not.

LIMITATIONS OF THIS CLASSIFICATION

One patient had a history of syphilis, a positive Wassermann and an aortic regurgitation; also a "rheumatic history," a continued fever, murmurs suggesting a mitral lesion and a pure culture of atypical streptococci in the urine. He seems to belong in two classes at once (Classes 1 and 2).

Three patients (two with necropsy) had a "rheumatic" heart and type of history; also a glomerulonephritis. There is good reason to believe that the same organism caused the two lesions. I have, therefore, classed these cases in the "rheumatic" (streptococcic) group despite the presence of a glomerulonephritis.

There are good grounds for holding that arteriosclerosis and glomerulonephritis may act conjointly and simultaneously to weaken the patient's heart. In my table the few cases which seemed to me of this type were grouped among the "doubtful cases."

Many believe that syphilis may cause arteriosclerosis. If so, Groups 2 and 3 of my table would in part coalesce. The "syphilitics" of this table are at any rate the relatively active cases with positive Wassermann.

SUMMARY AND CONCLUSIONS

1. Ninety-three per cent. of 600 recent hospital cases of failing heart have been found to group themselves without much resistance into four classes: rheumatic (streptococcic), syphilitic, arteriosclerotic and nephritic.

2. About 5 per cent. cannot easily be thus classified. The remaining 2 per cent. are "goiter" hearts.

3. In the 278 rheumatic cases females predominate: 170, or 61 per cent., to 108 males, or 39 per cent.

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4. Sixty per cent. of these rheumatic cases began before the twenty-second year. The typical rheumatic heart patient is therefore a young girl.

5. Of the seventy-four syphilitic cases 70 per cent. were in men; only 30 per cent. in women. The typical syphilitic heart patient is a middle-aged man (average age 47), with aortic regurgitation and no rheumatic history.

6. The ninety-three arteriosclerotic patients averaged 59 years of age. The 117 glomerulonephritic patients averaged 36 years. The arteriosclerotics are therefore twenty-three years older than the nephritic. The sexes are about equally represented in the two groups.

7. Diagnosis, prognosis and treatment are put on a more rational basis if we give up the terms "myocarditis," "cardiorenal" disease, "aortic regurgitation," "mitral regurgitation" or qualify them with an adjective like "syphilitic," "rheumatic" or "arteriosclerotic."

8. Practically all the stenoses belong in the rheumatic group.

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CARDIORENAL DISEASE

THE CLINICAL DETERMINATION OF CARDIOVASCULAR AND RENAL RESPONSIBILITY, RESPECTIVELY, IN ITS DISTURBANCES

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PHILADELPHIA

DEFINITION OF THE TERM "CARDIORENAL DISEASE"

The clinician encounters many cases, mainly in persons of middle age or older, in which evidences of cardiac weakness and other circulatory disturbances, such as high pressure, are associated with signs of failure of renal function or urinary indications of renal disease. When this combination of symptoms is of such character that the observer cannot readily assign to either the cardiovascular system or to the kidneys the preponderance of responsiblity, the term "cardiorenal disease" is often employed. The term, therefore, comprises cases of combined cardiovascular and renal disease without such manifest predominance of either as to justify a prompt determination of the one element as primary and important and the other as secondary and unimportant.

Among the pathologic conditions included in the term are three important groups: (1) primary valvular or myocardial disease with secondary renal disease; (2) primary arterial or arteriolar disease with secondary renal and myocardial disease, and (3) primary renal disease with secondary myocardial and vascular disease. It has long been an interesting and puzzling problem of the pathologists to determine the onset and initial stages of certain types of combined vascular and renal disease, and discussion of conflicting possibilities continues; but the clinician is called on to act at once

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in directing treatment in many of these cases when the clinical picture may lack clear indications to guide him.

A few examples of his difficulties will suffice to indicate the nature of his problems. A case of cardiorenal disease is mainly characterized by dyspnea, and in view of the evidences of cardiac and renal trouble, the determination of the responsible cause is difficult. Shall the physician rely on cardiac stimulation and hope for improvement from acceleration of pulmonary circulation, or shall he bleed or purge or sweat to remove the accumulated results of renal inadequacy?

A second case is one of stuporousness or actual coma in an aged person with evident arteriosclerosis, myocardial and renal disease. Shall the physician stimulate circulation with the thought that cerebral arterosclerosis and possibly beginning thrombosis are responsible or shall he direct his treatment toward combating a uremic condition?

A third case is one in which attacks of acute pulmonary edema have occurred in a person with high arterial pressure, myocardial disease and manifest nephritis. Shall treatment be used to strengthen cardiac power without regard to pressure, or shall the renal element be adjudged the serious fault and active elimination employed?

In still another case in which a general failure of health and nutritional disturbance occur in a person suffering from cardiac weakness, arterial disease and nephritis, the physician must decide whether cardiovascular stimulation or eliminative methods are requisite.

In any one of these instances, it might be suggested that the best way to treat the case would be to take into consideration all of its elements and employ such treatment as might reasonably seem effective against each of these. Such a course would perhaps appeal to one who has a merely theoretical knowledge of the difficulties involved, but never to a practical clinician

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whose whole training and experience would remind him that in complicated conditions successful treatment is always that which takes hold of the one important functional defect and corrects it. As well might one employ a combination of remedial measures to combat a case of generalized and complicated syphilis in which a recognition of the central cause and salvarsan or mercury were required!

As in other matters of treatment, the important underlying principle here is that the essential fault must be determined and if possible corrected. Any complicated combination of measures directed toward this and that is an indication merely of indecision and inefficiency. Effective remedial measures are almost always simple and direct. Let us take lesson from our surgical colleagues: A protracted medical treatment of vague gastro-intestinal troubles fails and the disease yields to the removal of a damaged appendix; an obscure case of illness, with occasional fever, emaciation and a variety of symptoms terminates when a calculous pyelitis is recognized and the stone is removed; a long-standing "rheumatism" of the ankles and knees subsides when fallen arches are supported. None of these ought especially be heralded as triumphs of surgery, but should rather be regarded as instances of previous failure of medical diagnosis.

Treatment directed toward symptoms or even functional disturbances without recognition of the real source or cause of trouble is almost sure to fail. Nowhere in my opinion is this more frequent than in the domain of cardiorenal troubles. One uses intensive treatment to modify blood-pressure, another attacks a supposed uremic trouble with active eliminative measures, a third believes the cardiac symptoms significant of the fundamental fault, and a fourth eases his conscience by a combined treatment of a variety of possibilities without subjecting himself to the test of determining what he really thinks is the fundamental defect.

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THE CLINICAL INDICATIONS OF CARDIORENAL DISEASE

The group of cases included under this term presents a varied systomatic picture. Dyspnea, continuous or paroxysmal, high arterial tension, a pallid (arteriosclerotic or nephritic) appearance, palpitations and sometimes substernal or precordial pain, sometimes edema of the extremities and effusions in the serous cavities, headaches, neuralgias and various cerebral disturbances, polyuria or reduction in the amount of urine, disturbances of vision, gastro-intestinal disorders and heaviness, stupor or even coma are among the prominent symptoms encountered. Physical examination discloses enlargement of the heart and evidences of cardiac weakness, sclerosis of the vessels, albuminuria and casts, in varying degrees of prominence. As the disease advances, increasing evidences of circulatory embarrassment on the one hand or of renal inadequacy on the other hand manifest themselves, and the terminal end may be quite clearly a circulatory or a renal death; but even up to the last there may be difficulty in determining the major fault. Particularly true is this in patients dying in coma when the possibilities of cerebral hemorrhage and uremia seem equally balanced, and in cases of severe paroxysmal dyspnea. From the very beginning, however, the physician finds it necessary to make a decision and direct treatment accordingly.

In reaching this decision he will find value in considerations that may be classified under the following heads: the history; the cardiac physical signs taken in conjunction with the blood-pressure and urinary examinations; the functional renal tests; the nutritional condition of the patient; ophthalmic findings, and therapeutic tests.

THE HISTORY

Of the three groups of pathologic conditions comprised under the general heading of cardiorenal disease, that which most frequently presents a clinical

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history of value is the combination of valvular or myocardial disease with secondary nephritis. Here a long-standing cardiac weakness is indicated by the history of onset after some severe infection, by the early dyspnea, edema, palpitations, arhythmia, etc., and by the discovery of marked physical signs of cardiac deficiency. Only in cases coming under observation late in the disease, in which marked evidences of nephritis have developed and in which the earlier clinical course is unknown, are the difficulties particularly great. Even such cases, however, present a sufficient predominance of indications of cardiac failure to emphasize the cardiac rôle in the clinical complex.

The difficulty is more decided in purely myocardial cases than in valvular disease. In the second and third groups of cases—those in which primary arterial disease has occasioned renal trouble or in which primary renal disease has initiated the whole series of lesions—the history is less significant. Sometimes, it is true, a history of renal trouble following an acute infection like scarlet fever, septicemia, pneumonia, or the like may stand out prominently; but much more often the beginning stages of nephritis are inconspicuous, and the history is entirely obscure. In the cases of primary arterial or arteriolar disease the onset and early course are so insidious that the history furnishes little clue to the nature of the disease. Formerly this group of cases was regarded as common and the picture drawn by Gull and Sutton of arteriocapillary fibrosis was accepted as adequate to explain many of the cases of cardiorenal disease which we are now considering. In more recent years the importance of renal disease as the initial cause of high arterial tension and of arteriosclerosis has been exaggerated to the practical exclusion of the older view. As usual the pendulum of opinion has swung too far, and there are abundant evidences that it is returning toward the older position.

If the pathologists and experimentalists have found it difficult to determine whether the renal or the vas-

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cular trouble is primary, how much more difficult is the clinician's task in forming an opinion of the relative significance of the two elements at a given time? The history of the cases can give only meager clues: sometimes the mode of life of the patient, his general appearance and the state of his blood-vessels taken in relation with the cardiac or renal conditions, a history of syphilis (especially in young cardiorenal patients) and other items of history, may furnish a certain amount of aid; but surer ground is reached when a study of the whole circulatory system is considered in relation with direct determinations of the renal function, with the urinary findings and with chemical examinations of the blood. These data will be discussed in succeeding paragraphs.

THE CARDIAC PHYSICAL SIGNS CONSIDERED IN CONJUNCTION WITH THE BLOOD-PRESSURE AND URINARY EXAMINATION

In Group 1, especially in valvular cases, cardiac enlargement and particularly enlargement toward the right is significant. The importance of this may be appreciated by contrasting a case of primary valvular disease marked by intense dyspnea with one of chronic interstitial nephritis attended by dyspnea. In the former right-sided enlargement, cyanosis, hepatic congestion and other indications of venous stasis direct attention to the heart; in the latter dyspnea is practically independent of weakness of the right heart, and right-sided enlargement is usually absent. Confusion is especially apt to occur when, as a result of renal hypertension, progressive enlargement of the left heart has finally occasioned mitral incompetency and a systolic murmur at the apex. Such cases are frequently regarded as purely valvular disease by those who overemphasize the significance of murmurs. In these cases the dyspnea (often quite paroxysmal), though primarily renal, may be in part cardiac. It is largely due to weakness of the left ventricle and to the sudden dis-

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proportion in the amount of blood thrown into the lungs by the right heart and that removed from the lesser circulation through the left side. Intense dyspnea of this type may be unaccompanied by any evidence of enlargement of the heart to the right.

A second point of importance in the physical examination is the character of the murmur heard over the heart. I am leaving out of consideration diastolic murmurs which are only rarely secondary to high arterial tension and renal disease, and wish to direct attention to the systolic apex-murmur that may be significant either of primary mitral regurgitation or of mitral incompetency secondary to high tension and left ventricular dilatation. In the latter case, I have quite commonly observed that the time and character of the systolic murmur differs greatly from that found in the former case. In primary mitral regurgitation, the systolic murmur always occurs in the early part of the systole, sometimes so early that it quite overshadows the first heart sound; while in the mitral leakage following continued high tension, the murmur is so late in systole that the first sound is heard an appreciable interval before the murmur and the second heart sound follows immediately after the murmur. Figure 1 will indicate the distinction. Not rarely in slow-acting hearts the lateness of the systolic murmur is at first confusing and suggests a diastolic murmur, but the second sound following immediately after it disproves this supposition. A late systolic murmur of this type is almost always significant of beginning cardiac failure in cases of hypertension. In a few instances, I have found it in mitral valve disease. Perhaps it was this murmur to which Austin Flint called attention under the name of prediastolic murmur and which he regarded as due to the back flow of blood in an atheromatous aorta just preceding the closure of the aortic valve. In view of present knowledge this explanation is, of course, inadmissible, and I do not wish now to discuss the cause of the time relations of

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the murmur. The reference to Flint is made only to indicate that he had doubtless observed the same murmur under the circumstances now under discussion. It should be added that the systolic murmur heard when the heart begins to fail in cases of hypertension is not always of this late character. In many instances it is precisely the same in time and quality as the murmur of primary mitral regurgitation.

Comparing blood-pressure with cardiac findings, the striking fact is the usual low tension in primary cardiac cases even when considerable renal disease has been superadded, and the reverse conditions in arteriolar and renal disease. In the latter conditions, even when terminal cardiac failure has advanced consider-

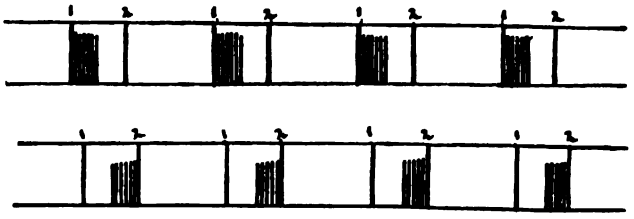

Fig. 1.—The upper figure represents the time relation of the systolic murmur of mitral regurgitation in disease of the mitral valve; the lower shows the time of the murmur (late-systolic) in cases of hypertension without valvular disease. The numbers 1 and 2 indicate the first and second heart sounds.

ably, arterial tension is likely to remain high. It has often been said that the arterial pressure may be low in arteriosclerosis and renal disease, and without doubt there are many cases in which it falls as cardiac weakness increases. The reduction in tension, however, is often less real than apparent because too frequently the systolic pressure alone is considered. The clinician may be deceived by reductions of systolic pressure from 180 to 140, 130 or even lower figures, when he has not noted that the diastolic figure has remained quite constantly at 110 or 115. Such values of the diastolic pressure in cardiorenal cases are practically always significant of arteriolar or renal disease rather than of primary cadiac disorders.

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The urinary findings in cases of primary cardiac disease contrast with those of primary renal disease mainly in their variability. When frequent examinations are made, the amount of albumin and the number of casts, red blood-cells or other cellular elements vary far more in the former than the latter, though without doubt considerable variations may occur in certain renal cases. However, no safe conclusion as to the relative importance of the cardiac or renal participation in the manifestations of cardiorenal disease can be drawn from the ordinary examinations of the urine. Just as the discovery of a systolic mitral murmur frequently leads to the erroneous impression that a case of nephritic hypertension with failing cardiac power is one of primary mitral disease, so the early discovery of albumin and casts may occasion the faulty diagnosis of primary nephritis in cases of valvular disease.

FUNCTIONAL RENAL TESTS

Among the functional tests in use at the present day are the following: the phlorizin test, the determination of the time relations and quantity of excretion of potassium iodid, sodium chlorid, milk-sugar, indigo-carmine and phenolsulphonephthalein. Each of these has certain advantages but I shall speak only of the last as my data regarding this are most abundant. The results obtained in cardiorenal disease are sometimes highly valuable, when due allowance is made for possible errors and for temporary variations in the degree of elimination. Among the causes of error one must consider especially the possibility of slow absorption in cases of edema and marked circulatory weakness, but with proper injection into the lumbar muscles this error is only occasionally considerable. If the normal elimination in two hours is placed at from 50 to 60 per cent. of the total coloring matter injected, the figures for primary cardiac disease with secondary nephritis are only moderately reduced, the findings varying from 30 to 40 or 50 per cent.; in primary renal disease,

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especially in certain advanced types, the figures fall to 20, 15 and even to 10, 5 and finally in some cases for considerable period before the fatal termination to 0. I find the test of less value in distinguishing primary nephritis from that secondary to cardiac weakness than in differentiating certain arteriolar cases from cases of primary chronic nephritis.

In making this statement, I must first of all admit that to a certain extent the claim to recognize primary arteriolar cases is an assumption; but clinicians will recall cases of continuous hypertension with excessive pressures varying from 200 to 300 systolic and from 120 to 150 diastolic, in which the physical signs indicate considerable diffuse arterial thickening (hard vessel-walls, increased substernal dulness, ophthalmic findings) and the symptoms are almost wholly those of hypertensive cardiac embarrassment. These cases may continue for years (six or eight under my observation in several) without any evidence of renal inadequacy.

Cases of this type occur in persons from 40 to 50 years old more frequently than in younger or older persons, and are more common in women than in men. The appearance of the patients contrasts sharply with that of cases of primary interstitial (or advanced types of parenchymatous) nephritis. They are frequently well nourished; often (especially women) somewhat fat; of fair color; the blood is usually normal in its hemoglobin content and the number of red corpuscles; there is little in the appearance of the patient to suggest grave illness. The non-coagulable nitrogen of the blood is within normal limits in these cases and not influenced by forced feeding with protein foods otherwise than in normal persons. The urinary examinations usually show mere traces of albumin and a few hyaline casts. The impressive facts are the continuous high arterial tension and the evidences of cardiovascular embarrassment and disease. Practically all of the cases which I have seen have been in the consulting

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room; there is little in the symptoms that I have recited to occasion such patients to seek hospial treatment. In other days one would have with little hesitation described such cases as instances of the earlier stage of arteriosclerosis, but in recent times the tendency to ally continuous hypertension with renal disease has caused many to overemphasize the renal element which undoubtedly exists. In view of the appearance of such patients, their subsequent history (ending in cardiovascular death) and among the clinical findings the ophthalmoscopic picture and the results of study of elimination through the kidneys, one may, I feel, with reasonable certainty separate these cases from primary renal disease. The elimination as is shown in the chart is practically normal or above normal. This is so strikingly in contrast with the condition in primary nephritis that I have placed the findings in the two groups side by side (Fig. 2).

A contrast picture is furnished by primary nephritis not only in the matter of phenolsulphonephthalein elimination but also in the appearance of the patient and the entire clinical course. I have in mind here only cases of primary chronic interstitial nephritis and certain late forms of parenchymatous nephritis which cannot be differentiated during life. In these cases the patient is usually much younger, between 20 and 50 years; his color is sallow, pallid, often almost icteroid; he is apt to be emaciated, the tense and tortuous temporal and brachial vessels stand out strikingly (partly as a result of emaciation), the blood is distinctly (often excessively) anemic; gastro-intestinal disturbances are frequent and a heavy coating of tongue and heavy or even fetid breath are noticed; a somewhat urinous or uremic odor may be present for long periods before actual uremia occurs. The blood-pressure is as high as in the average of the other group but less frequently attains the highest figures obtained in such cases. The ophthalmic findings are in distinct

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contrast. While hemorrhages may occur in both, the picture of so-called albuminuric retinitis is not seen in the arteriolar cases. The dictum of ophthalmologists that nephritic patients with hemorrhagic retinitis rarely survive for more than two years is doubtless correct for cases of primary nephritis, but must not be extended to the other group. I have frequently found, in the latter, survival for several years and in one at least have known recurring attacks with improvements by absorption of the blood in the intervals, running

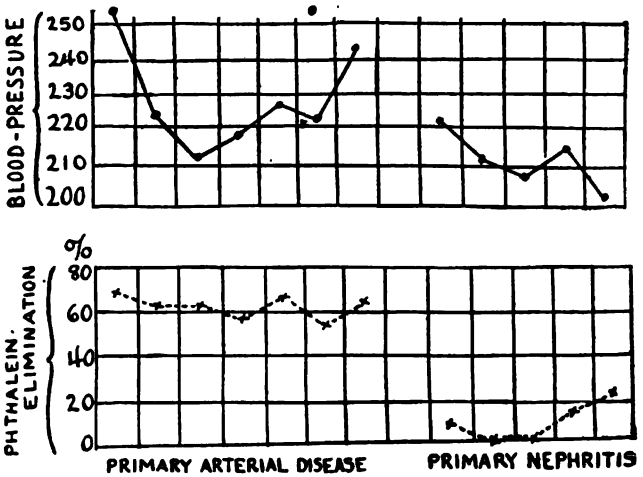

Fig. 2.—Seven typical cases of primary arterial disease with secondary nephritis and five cases of primary chronic nephritis are tabulated to show the hypertension in each group and the normal or excessive elimination in the former contrasted with the greatly reduced elimination in the latter.

over a period of thirty-one years. The patient eventually developed increasing evidences of the nephritic side of his malady, but nevertheless finally died a cardiovascular death. The phenolsulphonephthalein elimination in the primary nephritic cases is always markedly reduced and may be as low as 5 per cent. for long periods and sometimes may be nil for weeks before death. There is less frequently substernal dulness. Non-coagulable nitrogen in the blood

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customarily reaches high figures—from 70 to 80 and even 110 or 120 mg. per hundred cubic centimeters.

The terminal symptoms of these cases (Group 3) are very different from those in the arteriolar cases. Increasing headaches and disturbances of vision, recurring attacks of vomiting and finally pronounced uremia terminate the condition, commonly before the age when the other form of disease becomes manifest.

OBSERVATIONS OF THE QUANTITY OF THE URINE AND OF ITS PHYSICAL CHARACTER

These are important aids in the recognition of the type of cardiorenal disease. In the primary cardiac group the urine is almost always scanty and, in consequence, of higher color and specific gravity than normal. The variability of the chemical and microscopic findings has been mentioned, but it may be added that the urinary output and the character of the urine are closely dependent on the condition of the circulation from time to time. The renal element in these cases manifestly influences the condition of the urine far less than the cardiac and circulatory. In arteriolar cases considerable polyuria is a frequent but by no means constant condition—even when blood-pressure is enormous. The urinary findings are variable from time to time. Traces of albumin may occur at times and vanish at other examinations, tube casts are scanty as a rule and may frequently be absent. In other cases, constant albuminuria and cylindruria may be noted. One distinction in the urinary output and findings of this type of cases that has impressed itself on me is the variability in the urine of the day and night. More frequently than in primary nephritis the quantity of the night urine is greatly in excess of that passed during the day, and the specific gravity is considerably lower. This contrast in the night and morning specimen of urine may be a clue to the condition present. Somewhat the same observation, but rarely so striking, may be made in cases of the primary cardiac group.

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OPHTHALMIC FINDINGS

Sufficient has perhaps been said regarding the distinctions in the findings of the ophthalmoscope in primary arteriosclerotic versus nephritic cases. It may be added here that one feature common to both, hemorrhage, has been overemphasized. Too commonly this is regarded as synonymous with albuminuric retinitis and false deductions drawn. The discovery of marked arterial changes in the retinal vessels with or without hemorrhages should suggest a careful scrutiny of all the clinical features of the case to determine whether the nephritis is primary or secondary. Probably no single test applied to such cases exceeds a careful ophthalmoscopic examination in the reliability of the diagnostic and prognostic indications afforded by it.

THERAPEUTIC TESTS

Only the barest suggestions of the sort of information derivable from therapeutic tests need be made here; and it should be added that not too great a reliance should be placed on such data. In typical cases, however, of the three groups one may observe quite striking differences in the response to certain plans of treatment. The marked response of primary cardiac cases to digitalis and other cardiac tonics is sometimes fairly diagnostic in significance. Rarely ever does one see anything approaching this response in the other groups, even when second cardiac failure has become a marked feature. In the second group one finds the most satisfactory results from the diuretics of the caffein group. Rarely in other cases does one see the same enormous diuretic effect from caffein or theobromin salts. In the third group far more striking than in the other two diaphoresis—baths, pilocarpin, etc., sometimes yields satisfactory results. There are, of course, many intermediary cases in which therapeutic tests are confusing just as the clinical findings are of uncertain significance.

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ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. BROOKS AND CARROLL, CABOT AND STENGEL

Dr. E. Libman, New York: For some time past I have been classifying the more common cardiac lesions as follows: Two main groups of cases may occur alone or in combination. The first group is that of valvular disease, or valvular defect, and the second, endocarditis. The valvular defect may be due to the virus of rheumatism or of syphilis, or to atherosclerosis. The endocarditis may be acute, subacute, or chronic, and may occur in a previously normal valve or in a previously diseased valve. It may be due to the organism of rheumatism or it may be due to the various forms of streptococci, staphylococci, or other organisms. The subacute and chronic forms are practically always due either to the endocarditis coccus (so-called streptococcus viridans) or rarely to the influenza bacillus. I have seen three cases of infection of a syphilitic valve by the endocarditis coccus (streptococcus viridans). Taking Dr. Cabot's classification the prognosis in the various groups is, in general, as follows: In the group of valvular diseases due to rheumatism the outlook is governed by the degree of the lesion present, the condition of the heart-muscle, the mode of life of the patient, and the occurrence of various forms of endocarditis. In the syphilitic group the result will depend to a great extent on how much damage has been done before the patient comes under treatment, how much the coronary arteries are involved by the disease and what other lesions are present in the system. In the atherosclerotic group the prognosis depends to a great extent on the degree of loss of elasticity of the vessels and on the involvement of the coronary arteries, especially their orifices. In the nephritic group with hypertension, the prognosis again depends on the changes in the aorta and in the coronary arteries, the degree of the nephritis and the mode of life of the patient.

Dr. S. Solis Cohen, Philadelphia, Pa.: No subject was more neglected in the teachings of twenty-five years ago than etiologic diagnosis; nothing needs greater emphasis to-day. In my own classes I go a little further than Dr. Cabot has, not only with regard to the heart, but also with regard to the whole organism, to every form of disease and injury. I shall discuss, however, only the heart. Although we use the term diagnosis, this classification is important also in prognosis and in treatment. First we have the clinical diagnosis, let us say "cardiac decompensation." Then the anatomic diagnosis, let us say "mitral obstruction with insufficiency"—or "muscular disease," or "aortic" that is, "arterial disease." Here the distribution of the lesion is of great importance—as, for example, in Dr. Libman's illustration of involvement of the openings of the coronary arteries. Then comes the pathologic diagnosis. Have we a morbid process—intoxica-

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tion or tissue change—in progress, or are we dealing only with its results? We must discriminate infection with its intoxication and affection with its progressive tissue changes from the resultant infirmity—the impairment, the deformity, the interference with function produced by the scar-tissue and adhesion and muscular degeneration which remain when toxemia, inflammation and all active processes are past. The etiologic diagnosis comes next—syphilis, rheumatism, typhoid, whatever it may be. Only when infection or affection still persists does the etiologic diagnosis affect treatment. If they have ceased, we have to remedy, if possible, structural and functional results, but we cannot do this by treatment which concerns the infecting agent only. It seems to be a fact that in syphilis, the infection does persist, and the affection—the progressive tissue change—does continue, almost indefinitely.

Dr. Brook's paper on the syphilitic heart is thus highly important, in that it directs close attention to this often insidious and obscure form of cardiac disease. I would ask Dr. Cabot if, in continuing his valuable statistical studies, he will tell us something about the anatomic distribution in the syphilitic cases. I have been in the habit of teaching that the large majority of cases of "myopathic heart"—I don't like the term myocarditis, which means both too much and too little—are syphilitic in origin. Aortitis, too, is most frequently syphilitic; and neither luetic myopathy nor luetic aortitis is recognized as frequently as it should be. I have seen cases of both called asthma, and cases of aortitis frequently mistaken for aortic stenosis or aortic insufficiency, or, when anginoid or true anginal symptoms were produced, termed angina pectoris, but without recognition of the syphilitic origin. And other mistakes, too, are common. I have not, however, met many cases of pure mitral insufficiency that I could call syphilitic.

I agree with Dr. Brooks that mercurialization is the most efficacious treatment. Salvarsan helps; but if I had to choose between salvarsan and mercury, I would choose mercury. Fortunately, we can use both. My preference is to begin with inunction and push it to the point of mild ptyalism—to "touch the gums." Then the patient should be given a sweat-bath of some kind and put on iodids for a week or two. After this, salvarsan, preferably by intravenous injection, can be used. After a week or so, however, mercury is to be resumed, alone or in conjunction or alternation with iodid. The oral or hypodermatic method is now indicated. Salvarsan, too, may be repeated later. It is always important to follow or accompany the mercurial or mercurioiodic course with repeated sweat-baths. Bartholow advised pilocarpin, but heat usually answers. By persistence in this course, great

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amelioration, or as Dr. Brooks says "clinical cure" can be produced.

Dr. Charles Spencer Williamson, Chicago: Our success in these cases depends largely on the recognition of the underlying etiologic factors. There are three classes of cases which one finds in general hospital and dispensary practice for which Dr. Cabot has no place in his scheme of classification. 1. In a large number of cases of myocardial failure the right heart is exclusively or largely involved. These cases rise from pulmonary conditions such as emphysema, chronic bronchitis, occasionally long-continued asthmas, obliterative pleurisy and some other pulmonary conditions. The mechanism of these is essentially the same, that is, an interference with the flow of blood through the pulmonary capillaries, and hence an increased amount of work for the right ventricle. It is a sort of multiple pulmonary capillary stenosis, and in time leads to the well-known picture of failure of the right heart. 2. The group of hypertrophies of the right heart due to kyphoscoliosis. These are not so commonly seen here as in some European clinics, as in Saxony, for instance, yet they are far from rare. I do not think it is sufficiently appreciated that the "normal" ending of the kyphoscoliotic is, in most instances, due to failure of the right heart. The deformity, by obliteration of large parts of the lung with its contained capillary systems, leads to hypertrophy and, in time, stasis dilatation of the right ventricle, which marks the beginning of the end for the patient. 3. The group of the primary cardiac overstrains. I hesitate to mention this group because in many, possibly most of them, other factors coexist. Many show a positive Wassermann reaction.

Dr. Louis Faugeres Bishop, New York: The trend of medical thought is away from organic disease to a belief in general cellular disorder of all cells, but showing more in one part of the body than another. We are under the leadership of Vaughan and others, who are developing a glorified cellular pathology in continuation of the work of Virchow, which he began fifty years ago.

Dr. Robert N. Willson, Philadelphia: I hesitate to question the accuracy of Dr. Cabot's closing assertion that mitral stenosis has no other etiology than rheumatism; because I am reluctant to believe that I heard him correctly. From my own collection I could show him a number of specimens presenting high-grade stenosis of the mitral valve in the entire absence of rheumatism, tonsillitis, chorea, throughout the history of the case. Sclerotic involvements of the mitral valve are by no means rare in which neither syphilis nor rheumatism can be determined as a causative factor. I have seen more than one young adult of tuberculous parentage with all the classical signs of mitral stenosis; and in several instances have confirmed the diagnosis at necropsy. I refer

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only to cases in which rheumatism, chorea and tonsillar infection could be excluded from the history. With respect to Dr. Cabot's classification of heart affections, I confess I hear a new one proposed with considerable regret. It is tempting and in some features attractive. But it is neither accurate nor comprehensive. It encouraged the very slovenliness of diagnosis which he aims to prevent. One should be sure that there is a distinct advantage in new classifications before they are foisted on a long-suffering medical public. Thus Dr. Cabot insists on etiologic terms, and straightway himself uses three main divisions, not one of which is finally "etiologic." For example, who can at this day say just what the term "rheumatic" implies. Surely there could be no more vague term. Why not substitute the specific cause of the "arteriosclerosis" in Dr. Cabot's second division, if we are to accomplish his primary aim? What less definitive term could be used from the point of view of etiology than "nephritic?" How and why does nephritis cause heart-disease? If through mechanical causes, why not say so; if through a toxin, why not indicate the form of toxemia? Who knows after all that such a toxin finds its origin in the kidney, and not in the intestine or the liver? "Nephritis," therefore, would also seem to be an indiscriminate term for classification. "Syphilitic" alone is truly etiologic, and even this heading must include many cases that are "arteriosclerotic" and perhaps "nephritic" in origin. No room is provided for the congenital lesions, for the many mechanical cardiac cripplings secondary to such pulmonary involvements as emphysema and chronic tuberculosis. Few lung diseases leave a normal heart in their trail. Finally, the toxemias, such as tuberculosis, the cardiopathies of which have been so well described by Anders; of typhoid fever, the heart degenerations of which have been recognized for decades; of the pneumonias, the very definite cardiac muscular changes in which I had the privilege of demonstrating at some length. Dr. Cabot provides no classification that will properly include these and other cardiac involvements, perhaps the most striking of which are the heart paralyses of diphtheria. Perhaps it were better not to venture at all at this time of unrest and constant shifting from etiologic base to etiologic base. At least, if we do, the venture should be in the direction of a real etiology and not of vague names. For a time we can well afford to adhere strictly to (*a*) valvular and (*b*) muscular subdivisions, with a specific statement in each case as to the causal factor.

Dr. Graham E. Henson, Jacksonville, Fla.: I am glad to hear mercury and salvarsan spoken of as the treatment for lues rather than salvarsan and mercury. For so many years salvarsan and other agents have been trying to steal the laurels which rightly belong to mercury that it is gratifying

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to see the drug now come back into its own. While salvarsan is a valuable agent in the treatment of various syphilitic lesions, it should not be considered a substitute for mercury. I was glad to hear Dr. Brooks advocate the treatment of these syphilitic lesions with mercury in addition to salvarsan.

Dr. Richard C. Cabot, Boston: I have never seen mitral stenosis proved to be due to any cause except rheumatism. I believe it is due to rheumatism and to nothing else. Tuberculous heart affections are so rare that they may be disregarded. The terms "arteriosclerotic" and "nephritic" are local classifications, not etiologic. This is a pity, but till we know more of etiology we must use partly local terms. Among the causes of these affections we have lead, but we cannot make a separate division for it. Dilatation of the right heart secondary to lung conditions has, in my experience, always something else in the background, usually arteriosclerosis. Only a few cases of emphysema give a failing heart without arteriosclerosis. I doubt whether a sound heart can be broken down by muscular work alone. I heartily agree that treatment cannot always be based on these etiologic classifications, but must often rest on a symptomatic basis. What Dr. Libman calls "bacterial endocarditis" used to be called "ulcerative endocarditis." If there were any sharp and clear difference between this and the rest of the rheumatic group we should know it. So far I do not think satisfactory differentiations have been given. Most cases of the "cardiorenal" group should be classed either as arteriosclerotic or as renal. Cardiorenal is a bad term and only to be used when we cannot find another.

Dr. Harlow Brooks, New York: One of the most important prognostic factors is the early recognition of the involvement of the heart, because early treatment unquestionably spells cure. If not seen early, prognosis may be bad owing to the fact that the late lesions are largely fibrotic and therefore not capable of total eradication. Dr. Cabot's classification is a most valuable one, although it cannot as yet be very widely applied. Most of us now believe that a considerable percentage of hitherto unclassified myopathies of the heart are of syphilitic origin.

Dr. Alfred Stengel, Philadelphia: Dr. Cabot has denied stating that the etiologic treatment may be the only treatment to be applied. Improve the etiologic classification and it will lead to an etiologic treatment based on it. The kernel in the nut is that syphilis is an important cause of heart-disease and it should not be forgotten. Etiologic treatment is out of the question. Later on, however, it might lead to something else.

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END-RESULTS IN CASES OF GASTRIC AND DUODENAL ULCER

ELLIOTT P. JOSLIN, M.D.
BOSTON

In 1899 Dr. Robert B. Greenough and I[1] reported on the condition of 187 patients with gastric ulcer treated at the Massachusetts General Hospital for the preceding ten years. We were able to show that "of 114 patients, 80 per cent. were discharged cured or relieved, but at the end of an average period of five years only 40 per cent. remained well. The mortality at the same time (due to gastric disease) was 20 per cent. Among the men it was 30 per cent., in women 9 per cent. The excessive mortality of ulcer among men, its occurrence in life a decade later than in women, and the absence of fatal cases of hemorrhage in women, point to a difference of the ulcer in the two sexes. . . . The failure of medical treatment to effect a lasting cure in 60 per cent. of the patients indicates the need of surgical intervention in other than emergency cases of this disease." These figures aroused wide-spread comment, because gastric ulcer had previously been considered a disease in which cure was the rule.

Fifteen years have intervened since the preceding compilation. Revolutionary changes have taken place in the knowledge and in the treatment of the disease. Duodenal ulcer is now considered as frequent in occurrence as gastric ulcer. Undoubtedly, in the previous report, a considerable number of duodenal ulcers were classified as gastric. In this series an attempt has been made to distinguish between the

1. Greenough and Joslin: Gastric Ulcer at the Massachusetts General Hospital, 1888-1898, Am. Jour. Med. Sc., August, 1899.

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gastric and duodenal ulcers. This was difficult even with the knowledge gained in the operating-room. As a matter of fact, my personal division of the cases showed them to be within three of being divided equally. Surgery has wrought the other change in our attitude. Whereas, in the 187 cases occurring at the Massachusetts General Hospital in the ten years ending in 1898, but four patients were operated on, to-day operation is a common event. Justification, therefore, exists for another report on the end-results of treatment of duodenal and gastric ulcer, even apart from the fact that very favorable statistics concerning the present treatment of the disease are again being published.

The purpose of this paper is to call attention to the outcome, after the lapse of many years, of a group of cases of gastric and duodenal ulcer. It is not the intention to emphasize the medical or surgical treatment, but to show end results. Some of the cases were treated by me, but as a rule they were seen in consultation with physicians. The medical treatment of ulcer is sufficiently well known but not sufficiently well carried out.

It has been possible to ascertain the present condition of 91 per cent. of all the cases seen by me in private practice during the last sixteen years. As the whole value of the paper rests on this fact, we are more than glad to take this opportunity to acknowledge that so large a percentage of cases could never have been traced without the persistence of my secretaries, Miss Helen Leonard and Miss Florence Newnham. I am also greatly indebted to Dr. Hugh P. Greeley, without whom the cases could not have been selected and analyzed and to whose critical judgment I owe much.

METHOD OF SELECTION OF CASES

All cases showing digestive symptoms of any kind from 1898 to date, including even gall-stone cases, were collected from my records and analyzed for this

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report. This was necessary because to-day duodenal ulcer would be recognized in cases in which it was not recognized ten years ago. A number of cases of duodenal ulcer were thus found which were not originally so diagnosticated. The basis on which the diagnosis of ulcer rested was (1) the history, with especial attention to the symptoms of hyperacidity, pain, hemorrhage, perforation, the duration of the case and the after-history; (2) the knowledge acquired by surgery; (3) necropsy reports.

The total number of cases was 234. Table 1 shows the number of cases seen each year.

TABLE 1.—NUMBER OF CASES SEEN EACH YEAR

Year	No.	Year	No.
1898	3	1908	14
1899	1	1909	8
1900	3	1910	15
1901	4	1911	28
1902	9	1912	30
1903	17	1913	31
1904	12	1914	8
1905	23		
1906	14	Total	234
1907	14		

The present condition of the patient in 213 cases, or 91 per cent., is known.

SEX; AGE; AT ONSET AND DURATION

The number of male patients was 142, and the number of female patients was 92. These figures form an interesting contrast to the Massachusetts General Hospital series before cited, for in that series there were 5 females to 1 male.

The average age of the male patients when first seen was 45 years and 2 months, but this does not represent the age at which the symptoms of ulcer began. The average age of onset of the ulcer in the males was 38 years and 8 months. The average age of the female patients when first seen was 36 years and 4 months, and the onset began at 30 years and 10 months; in other words, symptoms had existed for five years and six months, and at an age eight years earlier than that of the males. The statement is approximately correct that six years intervened

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between the onset of symptoms of all the cases and the time they first came for treatment. Undoubtedly this interval was greater rather than less. The duration of the disease in patients at present not relieved is eleven years. The duration in many cases was, in the patients' words, "as long as I can remember," but these could not be included in our tabulation because a definite time of onset was not known. The duration between onset and operation in thirty of the eighty-two cases surgically treated was ten years. In other words, the cases came to the surgeon, at an average, four years later than to the physician. The importance of the long duration of this disease cannot be too much emphasized. It lends support to skepticism about the high percentage of cures so frequently reported by physicians and surgeons. Twenty-one of the patients were 60 years old or over when first seen. One patient was successfully operated on at the age of 86, for which the entire credit is due to Dr. E. A. Codman, who, remembering the patient's indigestion, discovered the ulcer during an emergency operation for a twisted ovarian pedicle.

SYMPTOMS

The severity of the disease is readily seen from the frequency of severe symptoms. Vomiting was present in 147 cases, 63 per cent. Pain existed in 184 cases, 74 per cent. Hyperacidity, as shown by the symptoms, or in a large number of cases by gastric analysis, appeared 134 times, or 54 per cent. Hemorrhage was noted in 71 cases, 30 per cent.; but this figure is low because these statistics of hemorrhage were compiled from facts learned at the first examination, whereas, occasionally, hemorrhage occurred later for the first time. Hemorrhage was occasionally observed at a time after operation when the trauma of the operation could be excluded.

Perforation developed 9 times, 4 per cent. Six of these patients were operated on, and two recovered.

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Of the remaining 3 patients, 2 died and 1 recovered, to die five years later of pulmonary tuberculosis. This patient, following perforation, coughed up pus for a considerable length of time.

Stasis was present in 41 cases, 17 per cent. To me it was a surprising fact that 3 of these patients with marked stasis, after periods of nineteen, fourteen and ten years respectively, must be considered as relieved and yet without surgical treatment.

RESULTS OF TREATMENT

The results of treatment are classified under the headings of "At Present Well," "Relieved," "Unrelieved," and "Dead." The term "At Present" is inserted because in too many cases in which the patients are considered cured, the ulcer recurs. Undoubtedly, a considerable proportion of patients now well will later develop symptoms. The term "Relieved" in this paper is liberally interpreted. Many patients recorded as relieved are merely relieved, and acknowledge that this condition is only attained by rest and a careful diet. In this group are also included many who before reaching this improved stage had a recurrence of symptoms. The term "Unrelieved" is self-explanatory. Under the heading "Dead," care has been taken to avoid the error of crediting deaths to medical or surgical treatment when these were simply intercurrent and had no relation to digestive trouble. There were 11 such instances. Two patients died of pneumonia, two of cancer of the colon and two by accident, while apoplexy, tuberculosis, cirrhosis of the liver, brain-tumor and cancer of the breast each claimed one.

Medical Treatment: The total number of medical cases traced was 131, of which 51 patients are well at present, 55 are relieved, 16 unrelieved, and 9 dead. Three of the 51 patients now well have had a recurrence of symptoms after being first treated, and of the 55 patients relieved, 19 have had such recurrence. In

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other words, of the 131 medical cases followed to the present time, 39 per cent. of the patients were cured, 42 per cent. relieved, 12 per cent. unrelieved, and 7 per cent. dead.

The causes of death of the 9 medically treated patients were as follows:

Cancer of stomach 2, cancer of duodenum 1, perforation 2, of which one was a typical case of paroxysmal vomiting in a child, hemorrhage 2, and inanition 2.

TABLE 2.—RESULTS OF MEDICAL TREATMENT IN 131 CASES OF GASTRIC AND DUODENAL ULCER

At Present	Number	Per Cent.
Well	51	39
Relieved	55	42
Unrelieved	16	12
Dead	9	7
		100

Surgical Treatment: It would be manifestly unfair to report the results of the surgical treatment without emphasizing that:

1. A surgical case means a medical failure. In all of the 82 surgical cases the patients were operated on because medical treatment had failed.

2. Among the surgical failures are necessarily included two types of cancer cases—those cases of ulcer in which the patients die, after months or years, from cancer, and also cases in which there might be a difference of opinion as to whether these cases should have been excluded from the ulcer series on the ground that they were cancer from the outset or had become cancer at the time of operation.

3. Several of the cases of perforation were transferred to the surgeon at a time when the whole responsibility really rested on the medical attendant.

4. A number of patients were transferred to the surgeon for operation debilitated by inanition or prolonged hemorrhages.

In drawing my own inferences from the surgical treatment of the eighty-two surgical cases, I should deduct from the group of twenty-six surgical deaths

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nine cases of cancer of stomach or duodenum for example, one of these patients at 75 years of age with a history of ulcer of twenty years' duration, showed cancer when operated on by the surgeon. He was given complete relief by gastro-enterostomy for a year and three-quarters and died painlessly six months later, yet that case although surgically classified should not be considered a surgical failure. I would also deduct two cases of perforation, because they occurred at a time when, even without perforation, the patient was *in extremis*, and also one case because of inanition of the patient. It is true that twenty-six of the eighty-two patients operated on are now dead, but with the deductions which I feel are justifiable, this number is reduced to 14, a surgical mortality of 20 per cent. In ten of the surgical cases, 12 per cent., the patients are still unrelieved. Thirteen, or 16 per cent. are relieved, though before reaching this half-happy stage after the surgical intervention, five had recurrence. Thirty-three, or 40 per cent. are now well, and of this number only three have had recurrence since operation. It will thus be seen that despite the handicaps which were heaped on the surgeon, his percentage of cures, 40 per cent., is approximately the same as that of the physician. If we discard the twelve deaths for which the surgeon might well not be held responsible, 47 per cent. of the surgical patients are well.

But I will now ask you to look at the matter from another point of view. If one should add all the surgical cases to the medical cases, for they were medical cases before they were surgical in this particular series, and then classify these surgical cases as medically unrelieved, we should then have 213 medically treated patients, of whom there are but 51, or 24 per cent., who recovered under medical treatment! The remainder, 162 patients, 76 per cent., were only partially relieved, unrelieved, dead, or forced into the surgeon's hands. It is my impression that this is the

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correct way in which to regard the medical treatment of gastric ulcer. In other words, medicine cures only approximately 24 per cent. of the ulcer patients, and of these there is a considerable chance for later relapse. Surgery helps out medicine and adds another 15 per cent. to those cured. In other words medicine and surgery together have given back complete health to 39 per cent. of 213 ulcer patients seen or treated by me in the last sixteen years.

TABLE 3.—RESULTS OF SURGICAL TREATMENT IN 82 CASES OF GASTRIC OR DUODENAL ULCER

At Present	Number	Per Cent.
Well	33	40
Relieved	13	16
Unrelieved	10	12
Dead	26	32

TABLE 4 (REVISED FROM THE FOREGOING).—RESULTS OF SURGICAL TREATMENT IN 70 CASES OF GASTRIC OR DUODENAL ULCER TREATED SURGICALLY *

At Present	Number	Per Cent.
Well	33	47
Relieved	13	19
Unrelieved	10	14
Dead	14	20

* This table was compiled from the foregoing table after the deduction of 12 deaths for which the surgeon was not responsible.

The causes of death in the surgical cases were as follows:

Cancer of stomach 7, cancer of duodenum 2, soon after operation 7, perforation 3, abscess of lung 2, empyema 2, pneumonia 1, pancreatic fistula 1, embolus 1.

It is noticeable that there is no case of jejunal ulcer; in fact, no patient with jejunal ulcer occurred in the series. In but five of the eighty-two cases was it necessary to operate twice.

The number of surgeons who operated on these 82 patients was 36. Two surgeons operated on 37 patients, and 4 surgeons on 15 others, while 30 patients were operated on by as many different men.

The type of operation was as follows:

Gastro-enterostomy	61
Infolding the ulcer, drainage, adhesions and exploratory laparotomy	15
Resection	3
Unknown	3

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It is noticeable in how few instances the ulcer was resected. I must record that one of the severest cases was the one in which fully one-third of the stomach was removed, and this operation was one of the most successful of the group. The case is particularly interesting in that the reason for this extensive resection was due to the report of an eminent pathologist that cancer was present, but on the following day his careful study of the section removed revealed no cancer. It is not appropriate for the physician to comment on the type of operation. The physician has enough responsibility of his own in the treatment of ulcer of the stomach and duodenum.

In Table 5 the combined results of medical and surgical treatment are given.

TABLE 5.—COMBINED RESULTS OF MEDICAL AND SURGICAL TREATMENT IN 213 CASES OF GASTRIC AND DUODENAL ULCER OBSERVED DURING THE LAST SIXTEEN YEARS

Present Condition	Number	Per Cent.
Well	84	39
Relieved	68	32
Unrelieved	26	12
Dead	35	16

CANCER SUBSEQUENT TO ULCER OF THE STOMACH AND DUODENUM

Twelve, or 6 per cent. of the 213 patients have up to the present time died of cancer. The statistics on this point, however, are complete only for the forty-six patients now dead. Of these, 26 per cent. succumbed to cancer. In other words, one out of every four of the patients with ulcer of stomach or duodenum, which have been followed to their death, died of cancer.

CONCLUSIONS

1. In a study made of 234 consecutive cases of gastric and duodenal ulcer seen in private practice during the last 16 years, 213 cases, 91 per cent., were traced to date.

2. Of these cases 142 were in men, 92 in women.

3. The average age in men was 45 years and 2 months when first seen, but the age at onset was 38 years and 8 months. The average age in women was

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36 years and 4 months, but at onset 30 years and 10 months. The average duration of the ulcer in the patients still unrelieved is eleven years; the average duration of the ulcer before the cases reached the surgeon, ten years.

4. There were 131 patients who were treated medically throughout, and of these at present 51, or 39 per cent., are well, 55, or 42 per cent., are relieved, 16, or 12 per cent., are unrelieved and 9, or 7 per cent., are dead.

5. Of the patients who were operated on when medical treatment had failed, 82 were traced and of these 33, or 40 per cent. are well; 13, or 16 per cent. are relieved; 10, or 12 per cent. are unrelieved, and 26, or 32 per cent. are dead.

6. Deducting 12 deaths for which the surgeon should not be held responsible there are 70 surgical cases in which 33 patients, or 47 per cent. are well; 13, or 19 per cent. relieved; 10, or 14 per cent. unrelieved, and 14, or 20 per cent. dead.

7. The combined medical and surgical results show at present: well, 84 patients, 39 per cent.; relieved, 68 patients, 32 per cent.; unrelieved, 26 patients, 12 per cent.; dead, 35 patients, 16 per cent.

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GASTRIC CANCER IN THE YOUNG

A STUDY OF SIXTEEN INSTANCES IN PATIENTS UNDER THE AGE OF THIRTY-ONE

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The sixteen instances of gastric cancer in the young forming the basis of this report were found in my study of the records of 721 pathologically demonstrated cases of cancer of the stomach at the Mayo Clinic and at Augustana Hospital. It is thought that their analysis will demonstrate certain facts of value in anticipating or detecting this grave malady at an age when it is not commonly suspected.

Those who wish to familiarize themselves with the literature on this subject may refer to the excellent monographs of Welch,[1] Osler and McCrea,[2] and Dock.[3]

A summary of previous reports on gastric cancer in the first three decades may be of service. Six instances (often rather dubious as to cancer) have been recorded below the age of 10. In the second decade, thirteen cases are described. In but eight of these were there reliable pathologic reports. In the thirteen instances occurring in the third decade, few descriptions are accompanied by pathologic findings. Many of the patients in this group, however, appeared to have been affected with a gastric malady, seemingly malignant.

1. Welch: Proceedings Boston Society for Medical Improvement, v, Appendix, p. 109.
2. Osler and McCrea: Cancer of the Stomach, Philadelphia, 1900, p. 16.
3. Dock: Am. Jour. Med. Sc., June, 1897, p. 665.

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INCIDENCE

The relative frequency of gastric cancer in the young varies with the individual series studied. In a small series, as, for example, the beautifully analyzed 150 cases of Osler and McCrea, the proportion was 4 per cent. In a large series, collected for statistical purposes from various non-related sources throughout the world, as in the 2,038 instances tabulated by Welch, the ratio is 2.8 per cent. In my own group of 721 consecutive cases, examined by a uniform method (and a distinctly American experience), the percentage was 2.2 per cent. Sex: There were nine females and seven males. Age: The youngest patient was aged 18; the oldest just past 30 years. The average age of the series was 27.8 years. Status: Twelve patients were married. In two instances (12 per cent.) there was a family or blood-relationship history of cancer. Only twice were more than ordinary indulgence in tobacco or alcohol noted. Apparently occupation had no etiologic significance.

DURATION OF ALL GASTRIC COMPLAINTS

Most useful facts are brought out by study of this phase (see table). It will be noted that the shortest time was four months, while in one instance the gastric disturbance had persisted for fifteen years. The average length of time of the disability was 4.2 years.

Consideration of the earlier part of those histories in patients exhibiting protracted gastric complaints not infrequently reveals the fact that there is in the early stages a different clinical presentation of the disease than is exhibited towards its end. It would seem that the observation of occasional cases of cancer in which the duration of the gastric history had been long drawn-out, doubtless led such clinicians as Dock[3] and Mathieu[4] to venture the opinion that can-

4. Mathieu: Semaine méd., 1895, p. 225.

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cer of the stomach in early life runs a somewhat slow course. This opinion appears well-founded if one considers both the "pre-cancerous" and the evidently cancerous portions of the history.

TYPES OF GASTRIC HISTORIES

In respect to types the histories divide themselves quite sharply into two groups: Group 1 includes cases in which there appeared a gastric affection, pernicious in nature and progressively downward in course, in patients in whom there had been no previous gastric ailment. Group 2 comprises a number of cases in which, previous to the time at which they came under observation for a gastric disease of a malignant kind, there had been gastric complaints which frequently conformed to the type which we call clinically "peptic ulcer."

Group 1.—Two of the sixteen cases studied fall into this class. The average duration of all symptoms was 4.5 months. In these two cases the disease was from its inception progressively and perniciously downward in course and type, and there was no alteration in the character of the affection. There were, clinically, rapid emaciation, continuous abdominal discomfort, early onset of vomiting, development of epigastric tumor and departures from the normal in the test-meal analysis (see table). Laparotomy revealed large, inoperable growths, with extensive involvement of the lymph-nodes and pancreas. One patient died within twelve days following operation; the other lived a year.

Group 2.—This includes fourteen cases. These patients had been affected for an average time of 4.8 years with some gastric malfunction. In type the early part of their affection had been roughly classed among the "dyspepsias." A careful analysis of the character of these dyspepsias reveals useful facts. In five instances (36 per cent.) the gastric complaint and

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course had fully satisfied the symptom-complex which we ascribe clinically to peptic ulcer. In four cases (25 per cent.) so-called ulcer features were definite at some stage in the early period (in one instance in this group there was frank gastric hemorrhage). In four other cases (25 per cent.) the long-term history previous to onset of evident malignancy was that of peptic ulcer of irregular type. In the remaining case gall-stone attacks were typical through four years, and the stones were later found at laparotomy.

The second part of the histories of cases making up Group 2 was typical of gastric malignancy. While this phase differed widely in character from the early manifestations, yet it could in nowise be distinguished clinically from the whole course of the ailment in the two cases making up Group 1. If one had not carefully analyzed the early histories of these fourteen cases in Group 2 he could have in no way showed their clinical variation from cases in Group 1. The period of evident malignancy in Group 2 averaged 7.8 months in duration. The most rapid progress was three weeks; that most extended nearly three years.

It might be useful to emphasize the fact here that of this group of gastric cancer cases in the young with long-time histories, 86 per cent. satisfied or approximated our present-day clinical complex of peptic ulcer at some time during a period averaging 4.8 years, previous to the time when the course became malignant; that during this time medical treatment availed nothing and the surgical opportunity for cure was usually neglected; that the cases in this group, due to some unknown cause, did not pursue a course of chronicity of benign type, but later evidenced malignant pointings, and that the malignant course of the cases in this group exhibited an average duration nearly half again as long as occurred in cases of Group 1 in which no previous gastric disorder had been observed.

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Appetite.—In six instances (38 per cent.) the appetite was poor. In the remaining cases it was usually fair.

Bowels.—All cases exhibited some degree of constipation.

Weight Loss.—In the two instances of short-term cancer, (the so-called "primary cancers"), the average loss of weight was 17 pounds. In the early period of the group of cases with long-term histories, weight loss generally occurred during the "spells" of the disability, but was rapidly regained during the succeeding quiescent stages. In some of these spells the weight loss ran as much as 35 pounds. In the late stage of cases of this type (the malignant period) the weight loss averaged 31 pounds. It was continuous and accompanied by other evidences of cachexia. Some rapid weight losses were observed, namely, 20 pounds in two weeks.

Abdominal Pain or Distress.—In some degree, this was noted in all patients. It was commonly located indefinitely in the epigastrium, but occasionally the complaint was of distress in the back or the high "pit." In two instances pains of so severe a degree and of such spasmodic character were noted that perforation was believed to have taken place.

In the two cases comprising Group 1 above ("primary cancers") the pain was never severe, never definitely localized, was continuous, but was generally aggravated by the ingestion of food or drink. In these instances the common pain relief was obtained by limiting the amount of ingested food, vomiting at the height of distress, and, occasionally, by alkalies.

Of the fourteen cases included in Group 2 above (those in which the patients had had gastric distress before malignancy became evident), twelve (85 per cent.) had pain in "spells" or "attacks." In seven instances, the pain at such times had borne fairly

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definite relation to food ingestion; in four instances, even when malignancy had supervened, the food relief of pain persisted. In ten cases former food relief of pain had changed to food aggravation of pain, as the malignant process became manifest. In this group of fourteen cases the common modes of pain relief were vomiting, lavage, limited or varied diet, alkalies, food intake and some form of opiate.

Abdominal Tenderness.—This was exhibited on palpation in all instances. In 38 per cent. it was located generally in the epigastrium. In three instances, the maximum tenderness was in the left epigastrium. In rare instances was abdominal tenderness, such as is characteristic of chronic ulcer of the perforative type, noted even when laparotomy showed that the peritoneum had become extensively involved.

Epigastric Tumor.—Tumor was palpated in six cases (38 per cent.) in the entire series (See Table). In but one instance was a large mass demonstrable. In the cases presenting no definite tumor, peculiar stiffness of the abdominal wall with a sense of deep resistance was frequently observed.

Four times free fluid was shown to be present in the abdominal cavity before laparotomy. These were inoperable cases. In three cases, metastases, as in the left supraclavicular region and the pelvis, were noted before operation. These patients had hopeless involvement.

Eructations and Pyrosis.—These were commonly noted, particularly when gastric motility had been interfered with.

Vomiting.—Vomiting, with or without nausea, was observed in all the cases at some time (usually in the terminal stage) in the course of the disease. In the two "primary cancers," vomiting came on daily soon after taking food, was large in quantity, rancid in odor, but never "coffee-colored."

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In the fourteen instances in which malignancy had terminated a long-term gastric history, vomiting occurred from one to eight hours after meals; in but one instance was it "coffee-colored;" in all instances it contained food particles, was of a rancid odor and relieved abdominal distress. In eight cases "delayed" vomiting was observed. Such sign was usually associated with pyloric stenosis and huge, dilated stomach.

LABORATORY DATA

Blood.—In the fourteen instances in which the hemoglobin was estimated, it averaged 66 per cent. The range was from 25 per cent. to 70 per cent.

Stool.—In ten instances (62.5 per cent.) altered blood was chemically demonstrated by the benzidin or the guaiac tests.

Test-Meals.—In fifteen instances facts of much interest were obtained by this mode of examination of gastric function. One case (No. 14, see table) returned no information by test-meal analysis because the stomach-tube could not be advanced beyond the cardia. There was obstruction due to extensive local growth.

Gastric Emptying Power.—In eleven cases (73 per cent.) motility was interfered with and there was retained food at the end of twelve hours. In such instances, dilatation of the stomach of various degrees had invariably occurred.

Gastric Acidity.—In no case was achylia shown. The average *total acidity* was 59. It ranged from 28 to 64.

Free Hydrochloric Acid was absent in but one instance. This was a case of fulminant, primary cancer. The average free hydrochloric acid estimation for the entire series was 26. It ranged from as low as 3 to as high as 60. The highest free hydrochloric acidities were noted in association with large, cancerous ulcers.

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Combined hydrochloric acid and acid salts averaged 18.1. It ranged from 0 to 50.

Lactic acid was demonstrated by the modified Uffelmann test in six cases (40 per cent.).

Altered blood was proven by chemical test in gastric contents twelve times (80 per cent.).

Microscopic Examination of Unfiltered Gastric Extracts.—In but six instances (40 per cent.) were organisms of the Boas-Oppler group definitely identified. In eight cases (53 per cent.) yeasts and sarcinae were present. Microscopic food bits were recognized in nearly 90 per cent. of instances.

THE LAPAROTOMY FINDINGS

Two cases had been explored before coming to us. Both the patients had been operated on within the year. At both abdominal sections the surgeon had made a clinical diagnosis of "benign" gastric ulcer of the chronic type, yet both of these patients were dead from inoperable, general cancer before a year had elapsed! The resection of the ulcer or the microscopic examination of a bit of extirpated tissue at the time of the initial laparotomy doubtless would have made known earlier the prognosis and have prevented further surgery. It may have saved life.

Location of the Malignant Process.—Abdominal section revealed five instances in which the pylorus was involved; nine cases in which the lesser curvature and some part of the surface of the viscus were affected; one instance of infiltration at the cardia, and one case of general carcinosis.

Lymph-nodes had been invaded in fourteen out of the sixteen cases in this series. Nine times secondary growths were demonstrated in the liver, pancreas, omenta or pelvic organs.

Character of Neoplasms.—In eight instances, extensive ulcera carcinomatosa were present. They were of the medullary type. In the remaining cases, adenocarcinomatosa of the common type were demonstrated.

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OPERATIVE PROCEDURES AND OUTCOME

In four instances exploration only was possible. In five cases some form of resection was performed with or without gastrojejunostomy. In the remaining seven patients "drainage operations" to fit the case at hand were devised.

Nine patients died within one and one-quarter years following operation. To the other patients of this series was granted a lease of life of from two to more than five years.

122 South Michigan Boulevard.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. JOSLIN AND SMITHIES

Dr. J. N. Hall, Denver: There are certain chances of error in the diagnosis of gastric ulcer that do not come to one's attention unless the cases come to operation. In case hemorrhage occurs it draws attention to the possibility of ulcer and makes the diagnosis easier. I recently had a case showing pain, hyperacidity and distress and I found that the patient had had trouble ten years before, I believed that this was undoubtedly a recurrence, and had expressed that opinion to the surgeon. At exploratory operation we found the marks of an old ulcer 4 or 5 inches from the pylorus, a condition which it would have been impossible to diagnose without operation. The acute symptoms were caused by a chronic intermittent pinching of the pylorus in a Treitz's hernia which caused the blood to leak through into the stomach. In another case there had been a long-continued history of gastric symptoms in a patient who came from the country and who was a hard drinker; when I saw him he was nearly moribund from a violent hemorrhage believed to be from ulcer. I found it due to a thrombosis of the superior mesenteric artery, associated with cirrhosis of the liver which had followed alcoholism. In another case there was a chronic pinching of the superior mesenteric vessels under the root of the mesentery. For a long time there was slow bleeding, leading us to believe he had an ulcer, but none was found. I have seen two or three cases from three to six months after appendicitis with symptoms of ulcer caused by dragging down of the pylorus by the omentum. Some of these cases have obscure and continuous pain and it is difficult to figure them out. Time and again, I have found a minute hernia, not larger than a grain of wheat, and these slight hernias often give the symptoms of pyloric ulcer. This is probably caused by chronic reflex irritation of the

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stomach which continues until symptoms of ulcer appear. Again we see patients with the severe pain associated with ulcer, and with jaundice. Two or three operations have been performed with the idea that we were dealing with gallstones, because of the pain and jaundice, and the surgeon was chagrined when the real condition was found to be duodenal ulcer. In such cases the large duodenal ulcer had spread and compressed the common bile duct.

Dr. F. B. Lund, Boston: Dr. Joslin's paper gives a good idea of the ultimate results in surgery of the stomach. I do not think, however, that he ought to speak of a surgical mortality of 20 per cent. in gastric ulcer without making it plain that that is not the operative mortality. The operative mortality in my own cases is 5 per cent. The function of the surgeon in gastric ulcer is to interfere in cases which have resisted medical treatment and alter the conditions so that the ulcer may heal. This good end is accomplished in from 60 to 80 per cent. of the cases that are operated on. I understand that Dr. Joslin reported a case of duodenal ulcer in which the patient died in the sanatorium six months after the operation, as a surgical death. To my mind, this was not a surgical death, but a surgical failure; surgical interference failed to cure the ulcer and the patient died in six months, not because of, but in spite of it. Only those who die while still in hospital should be called surgical deaths. This, of course, would make the surgical statistics look very much better.

Dr. Frank Billings, Chicago: I think Dr. Joslin's statistical paper is only of relative value. Dr. Joslin acknowledges that the diagnosis of ulcer was not made in some of the earliest cases seen and that some of the patients were seen only in consultation. Therefore, there may be a question of diagnosis in some of the series. Thirty surgeons operated on thirty patients. How many physicians managed the medical treatment? What operations were performed? What was the medical management? If medical treatment failed, why? Of what did the patients surgically treated die? My experience is that ulcer of the stomach is usually mismanaged medically by the average practitioner. Statistics, to mean anything of value, must be more explicit in details of both medical and surgical treatment.

Dr. J. A. Lichty, Pittsburgh, Pa.: It seems from Dr. Joslin's paper that neither the medical nor surgical treatment of ulcer is altogether ideal. From his paper we learned that 43 per cent. of the 213 cases were supposed to be cured. This is, of course, a low percentage of cures in a condition which is, after all, not so frequently fatal. This may be explained by the facts submitted. It seems the patients were not seen by the internist until the ulcer had run a course,

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on an average, of five and one-half years, or by the surgeon until the ulcer had run a course, on an average, of ten years. It is to this part of Dr. Joslin's paper I wish to direct attention—the necessity for early recognition of gastric and duodenal ulcer. The low percentage of cures is due more likely to the length of time which expires before any proper treatment is undertaken. The irreparable damage occurs before the internist sees the patient and not during the interval between the internist and the surgeon. In other words the patient likely lost his chance for cure before either internist or surgeon saw him. This is a difficult problem to meet. It is not always the fault of the physician. The patient will carry soda-mint tablets and alkaline powders for years before consulting a man who is capable of diagnosing gastric or duodenal ulcer, and it is not the fault of the laity alone; even physicians themselves in their own cases pursue the same course. In our teaching in medical schools, the symptoms of so-called "dyspepsia" should not be considered lightly, but should be looked on always as the evidence of some pathologic condition until the contrary is proved. If all the means at our disposal are employed it is not so difficult to make a diagnosis in early cases of acute or open ulcer. It is only after ulcers have been present for some time that they become so difficult to diagnose. We have now many tests, as for occult blood in the stools, the string test, roentgenoscopy, gastroscopy and others. If all the tests are employed and the patient's history carefully studied the diagnosis can be made easily in the early cases of open ulcer. I am sure this 48 per cent. of cures can be brought up also by teaching the laity to apply early for treatment in cases of gastric disturbance. If patients are seen during the first month or during the first two or three, or even five months, and proper medical treatment is instituted, I am sure more than 48 per cent. will get well. In reviewing my cases for the study of hemorrhages in both gastric and duodenal ulcers I have been impressed by one point in particular. Early cases giving symptoms of one, two or three months duration only, usually had no complications and got well on medical treatment promptly applied. The results were good. On the other hand, when the symptoms extended over two, three or even twenty years the complications were responsible for the chief symptoms. The diagnosis was difficult, medical treatment a failure, and unfortunately surgical treatment frequently not so successful as might be wished.

Dr. Alexander Lambert, New York: Did Dr. Joslin try to calculate the end-results with the two surgeons who had 34 cases and the thirty surgeons who operated in the 31 cases? What was the difference in results between those who were in the habit of performing these operations and those who performed them relatively infrequently? It is

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known that the gastro-enterostomy opening into the stomach is apt to close if the pyloric opening remains patent. It is only when the pylorus is definitely stenosed that the gastro-enterostomy remains open. If 45 per cent. of the patients operated on, and about 50 per cent. of all patients treated medically remained unimproved, it must show that neither medically nor surgically have we worked out a successful treatment for these chronic ulcers of the stomach. Of course there is no question that in those old chronic ulcers in which there is scar tissue and a stenosis or deformation around the pylorus and a definite mechanical obstruction at this point, surgical procedure is the only method by which relief may be obtained. In other chronic ulcers, however, without the deformation of the stomach, so many different kinds of medical treatment have been tried that it is impossible to say, by any given set of statistics, whether or not really purposeful medical treatment had been accurately carried out. Until we are able to answer the questions of etiology of duodenal and gastric ulcer and base our treatment on this knowledge, it does not seem to me that we will be able to obtain much better results than those that are reported by Dr. Joslin, for if medical treatment gives but 39 per cent. of so-called cures and surgery gives but 45 per cent., there is such little difference between these results that it cannot be said that either one or the other offers much advantage, and neither medicine nor surgery has, as yet, worked out a proper method of treating these ulcers of the stomach and duodenum.

Dr. F. A. Speik, Los Angeles: What Dr. Billings and Dr. Lambert said is true. Patients do not pay enough attention to the early symptoms of ulcer, but it is also true that the physician whom they consult early does not work hard enough to determine whether the diagnosis should be of gastric and duodenal ulcer. Diagnoses are made of indigestion or dyspepsia and the patient is put off with palliative treatment. Many of Dr. Joslin's cases came to him eight or nine years after the onset. They surely consulted some physician before they did him, but the correct diagnosis was not made. Dr. Joslin's medical failures are not due to incorrect medical treatment, but they are due to the lack of early recognition, and therefore due to the lack of proper treatment. Many of his cases presented surgical complications when they came to him. Surely he cannot call all surgical cases medical failures, because not only are the ulcers not recognized and not treated, but also many are latent until some such surgical complication as mechanical obstruction, perforation, perigastric adhesion, etc., takes the patient to the physician. These must be recognized as surgical cases and not treated medically. There are definite indications for medical treatment and relative and absolute indications for surgical treatment. The surgical cases are those that may be

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relieved mechanically, such as perforation, which demands immediate diagnosis and operation, pyloric obstruction with actual cicatricial narrowing, with obstruction of high grade (but pyloric closures due to inflammatory swelling and spasm are medical cases), perigastric adhesions, hour-glass stomach, etc. Hemorrhage in 97 per cent. of the cases calls for medical treatment. In a medical case a gastro-enterostomy does not necessarily heal the ulcer. If the pylorus is patent the gastric juice will continue through it and take off the granulation tissue and the ulcer does not heal. In Dr. Sippy's clinic, motor meals on the gastro-enterostomized stomach show that the stomach does not empty itself faster than normal. Our failures in gastric and duodenal ulcer are due to the lack of early diagnosis and the lack of an energetic medical treatment. The medical man should work harder to make the early diagnosis of ulcer and should also pay more attention to detail in his treatment; then there will be fewer medical failures.

Dr. Allan A. Jones, Buffalo; There should be no unpleasant contention between the medical and the surgical men with respect to the care and treatment of gastric and duodenal ulcer. I often wish that medical men could operate, not that they would operate so often as surgeons do, but that they might apply this form of mechanical therapeutics. What is surgery but mechanical therapeutics? It is not a question of medicine or of surgery but of the accurate diagnosis in a given case at a given time and in a given condition. If the patient does not make satisfactory progress under medical treatment then one should resort to surgical treatment. Statistics are apt to be misleading and are sometimes useless, but if Dr. Joslin's paper shows anything it is that our best results follow medical treatment, but that at the proper time and under proper conditions surgery must be chosen. So far as the results of medical treatment in gastric and duodenal ulcer is concerned, the real and only valuable statistics we could compile would be compiled by personal supervision of every patient in the hospital kept under the immediate care of special nurses, as the control of the diet is most important. It is difficult to control the patient's diet when he is out of the hospital. Von Leube, some years ago, reported 556 cases in which the treatment consisted of absolute rest in bed, a milk diet, the application of poultices over the epigastrium and the administration of little or no medicine, and in these there were 95 per cent. of cures. I do not know the end-results in this series of cases, nor do I know how many recurrences there were, but there was probably a large number. The study of the end-results in a series of cases, as made by Dr. Joslin, is timely and important.

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Dr. J. R. Verbrycke, Washington, D. C.: I call attention particularly to the thread test, the benzidin reaction for occult blood and the roentgenogram. With a few exceptions I hold the clinical history subservient to these tests. A thread smeared with blood does not always positively indicate an ulcer, but small localized spots always in the same place on several threads has in my experience been almost infallible. I rarely make a positive diagnosis of ulcer without a positive benzidin reaction. When we learn the value of these tests as well as their limitations, we will make much earlier diagnoses and so secure better end-results. I am still finding more gastric than duodenal ulcers. The number of duodenal cases has markedly increased, but through our increasing facilities for diagnosis the gastric ulcers have kept pace. By the thread and the roentgenogram—the only reliable means of localization—I am finding many to be on the lesser curvature and have encountered about thirty in that location in the past two years. The localization of ulcer is important both for prognosis and for the treatment. A duodenal ulcer operated on with gastro-enterostomy and closure of the pylorus usually gives spectacular results, while, on the other hand, ulcer of the lesser curvature may not only be cured by operation but the symptoms may be aggravated unless the ulcer is excised. Our criterion for cure should be just as strict as our endeavor is earnest to make a diagnosis in the first place. It is not sufficient that the patient does not have symptoms. I always have the patient report, after his treatment, once a month for a year bringing a specimen of stool to be examined for occult blood. Occult blood often appears months before a return of subjective symptoms. If the patient has no return of symptoms or occult blood for twelve months, we can call him cured.

Dr. Anthony Bassler, New York: Until more is learned of the etiology and pathology of ulcers, statistics on results of treatment will be useless. To say so many ulcers have been treated either medically or surgically and to give results without discussing the etiology and the varied pathology of ulcers is holding the subject back. I think that Dr. Joslin's statistics present too few cures by both the medical and surgical methods of treatment. I agree with Dr. Billings and Dr. Lambert; the subject cannot me presented *in toto* from the medical or the surgical side alone. The unfortunate status of affairs in this condition makes one case of ulcer in which the etiology and pathology have been worked out of more worth than statistics on a thousand treated in which neither one of these is mentioned. It is probable that so far as results from treatments are concerned, division can be made between soft and hard forms, for in my experience it

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depends on the absence or presence and extent of fibrous tissue and the character of cell infiltration whether medical or surgical measures are successful. Our knowledge of etiology, the old divisions of pathology, the overusing the length of clinical course for differentiation between acute and chronic forms, and even the revealments of the operating-room are still far short of what we must learn properly to understand gastroduodenal ulcer.

Dr. George Douglas Head, Minneapolis: How long a time have these operated patients been under observation subsequent to operation? We all know that the history of gastric and duodenal ulcers is one of remissions and exacerbations. A tremendous amount of statistical material has been brought to our attention from the surgical clinics during the last few years purporting to give the operative end-results of gastric and duodenal ulcer after one, two or three-year periods. In discussing the cure of gastric and duodenal ulcer, we as medical men are thinking in the terms of five, ten or even more years and our statistics are based on these figures, while the surgeons are giving their results in terms of one, two, or at most five-year periods. No surgical statistics exist showing the results of operative treatment over a ten-year period. In order intelligently to compare the end-results of the surgical and medical treatment of gastric and duodenal ulcer the same standard of time interval must be adopted by both surgeons and internists. Over how long a period of time were Dr. Joslin's series observed subsequent to operation? We must not deceive ourselves in the analysis of statistical material offered in proof of one method or the other for the cure of gastric and duodenal ulcer. We must approach the whole subject in a broad but scientifically critical spirit.

Dr. J. D. Dunham, Columbus, Ohio: The occurrence of gastric cancer in patients under 30 years of age is quite infrequent. I have seen three, in two women and one man, aged 18, 24 and 30 years, respectively. In every instance there was increased hydrochloric acid and the total acidity was increased. All were of the fulminating type. All three cases were proved by operation and histologic examination of the specimens to be true cancer.

Dr. M. H. Fussell, Philadelphia: I have not heard a word spoken of indigestion; it has probably been purposely left out. Yet I would venture to say that practically every patient whom Dr. Joslin has seen was treated for indigestion long before it was thought that the condition was gastric or duodenal ulcer to be treated either medically or surgically. Many cases will continue to be treated for flatulence, epigastric pain and disturbance and for indigestion until they are far beyond hope from medical treatment and in many cases

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from surgical treatment. It is a fact that numerous conditions bring about symptoms which are called indigestion. The functional cases of indigestion are not due to any surgical condition whatever. In such conditions as gastric ulcer, infectious gall-bladder disease, chronic appendicitis, carcinoma, and others, the true condition is often not recogized until the patient is far beyond the help of either medical or surgical treatment. When one sees a patient with what is commonly called indigestion, that patient should be gone over carefully from head to foot to find out just what is the matter. Then treatment should be according to the indications. I think we are entirely unjustified in treating these case with alkalies and other internal remedies for months and years until they become difficult to diagnose. It is not the early cases as described in the text-books that are hard to diagnose but the border-line cases. When a patient has been given all the advantages of medical treatment and does not improve it becomes our duty, after a reasonable period, to have an exploratory operation to find out what is the matter, for an exploratory operation is less dangerous than long-continued medical treatment that is giving unsatisfactory results.

Dr. G. M. Rector, Columbus, Ohio: I also want to emphasize that point and insist on the early diagnosis in these cases. I would also mention a possible cause of ulcer—pyloric infection and the production of a ferment which destroys the tissues. Raise the resistance of the patient by increasing nutrition. This brings up the consideration of the motor function of the stomach and its ability to deliver food, which also brings up the point of the necessity of surgery at times. In the process of digestion we may say that the content of the stomach is water. The state of pressure from the diaphragm below and from the water above brings up the question of equilibrium or balance. The contraction of the stomach is also of great importance. Therefore, when obstruction at the pylorus exists, or after a gastro-enterostomy has been done, it is a question of musculature that is important. If we must resort to surgery the most important thing is drainage. If we can mechanically restore the musculature and effect proper drainage surgical treatment is not necessary.

Dr. Elliott P. Joslin, Boston: I agree with Dr. Lund that if the surgeon gets his cases of gastric and duodenal ulcer in a favorable condition he may obtain from 90 to 95 per cent. of recoveries. Dr. Lichty hit the point when he said that cases of ulcer would do better if treated early. In my series of 213 successive cases, there was an average history of six years of discomfort before seeking treatment. I hope no one else will report a series of cases coming to treat-

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ment after having suffered so long. I purposely did not attempt to draw comparisons between the thirty patients operated on by thirty surgeons and the thirty-seven operated on by two surgeons, because the number was too small. Probably four-fifths of the surgical cases were treated during the last three or four years; consequently the surgical end-results showing 47 per cent. of cures cover a far shorter period of time than do the medical end-results. The statistics, therefore, are favorable to the surgeon. Dr. Billings criticizes the value of these statistics because the cases have been treated by many medical men and necessarily (?) show very poor results. In the last series of cases which I reported some sixteen years ago, with Dr. Greenough, the criticism was likewise made that the results were unusually poor. In that series 114 cases were reported and it was stated that 80 per cent. were discharged from the hospital cured. At that time the Massachusetts General Hospital was under the dominating influence of two of the best men in medicine in America—F. C. Shattuck and R. H. Fitz—and there is no doubt but that these men carefully treated the patients with ulcer of the stomach. Yet when we came to analyze the 80 per cent. of cures and ferreted the patients out after five years, we found that only 40 per cent. were well or even relieved, quite as in this recent series. There is little doubt that if Dr. Billings studies the records of the Chicago hospitals, he will find 80 per cent. of the patients with ulcer of the stomach or duodenal ulcer have been discharged as cured, but if he should be able to follow 91 per cent. of the series after five years have elapsed, he would probably discover that the percentage of cures had dropped far below that figure. Is it not proper to ask Dr. Billings to present a similar series of 234 or more cases of gastric and duodenal ulcer and to trace out the end-results of 91 per cent. of them after a period of five years? Should this be done, I think he would allow that our statistics are correct. In the paper we did not attempt to discuss the medical treatment of ulcers, but rather to show what happened to patients who had had the disease, in the hope that we all might treat our cases better.

Dr. Frank Smithies, Chicago: The whole subject of gastric ulcer is in a state of transition. Confusion arises from medical men trying to interpret surgical statistics, and vice versa. The life history of chronic peptic ulcer is one of periodicity of symptoms and signs. It is a disease prone to recover and recur, seemingly quite irrespective of what type of medical treatment we use. Many cases called "medical gastric ulcers" have been shown by laparotomy not to be ulcers at all. This is especially true in persons under 30 years of age. In these patients, practically the same clinical

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picture is presented when the lesion is in the appendix or gall-bladder. In this event pyloric spasm, and vagotonic hyperacidity are responsible for the discomfort. Unfortunately, the statistics of peptic ulcer have been confused by this false ulcer group. "Medical ulcers," so-called, do, however, occur. They are apparently, in their life history, quite a different pathologic process from the chronic ulcer. Hence, this type of ulcer cannot in any way be compared, statistically, with the "surgical" ulcer. A medical ulcer is something that can rarely be seen or felt and manifests itself only by its symptoms, whereas, a "surgical" peptic ulcer can be seen and felt, examined pathologically, and definitely described and recorded. It would seem that Dr. Joslin is quite justified in giving the statistics that he has presented. It shows us our limitations in the subject. He has gone quite as far as possible in the comparison of things, which, from their different clinical and pathological nature, it is impossible to compare. Concerning the value of the occult blood-tests and the "string test," both these maneuvers may lead us to make grave mistakes, unless carefully checked. I have used three hundred strings. In 167 instances, peptic ulcer was proven operatively. In but seven instances, were the findings suggestive of a "positive" string-test. When it is recalled that ulcers only bleed intermittently, it will be seen what a factor of chance there is in relying on this test for useful, clinical information. Tests for blood in the feces by means of guiac or benzidin must be very carefully interpreted. Patients on a meat-free diet may give typical reactions if they are eating chlorophylaceous vegetables, or food rich in iron compounds.

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FOCAL INFECTION

ITS BROADER APPLICATION IN THE ETIOLOGY OF GENERAL DISEASE

FRANK BILLINGS, M.D.
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Circumscribed and confined infection, commonly expressed as focal infection, has long been recognized as an important etiologic factor in systemic disease. Yet as a principle it has not received sufficient attention from practitioners. In my opinion focal infection is very frequently related to local and general disease. Apparently it is an important factor in some systemic diseases, heretofore unsuspected.

For several years, the medical clinic of Rush Medical College and the Presbyterian Hospital has furnished a large number of patients suffering from chronic infectious endocarditis of the malignant type (*Streptococcus viridans*), arthritis deformans, rheumatic fever, nephritis acute and chronic, chronic myocarditis, exophthalmic goiter, cholecystitis, ulcer (peptic) of stomach, diabetes mellitus, etc. In addition to the usual clinical and laboratory investigations by the members of the clinic, collective and cooperative research has been carried on in connection with the workers of the Otho S. A. Sprague Memorial Institute and the Memorial Institute for Infectious Diseases. The "team work" has been truly coopera-

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tive and the results thereof have been published from time to time (Billings,[1] Davis,[2] Jackson,[3] Rosenow[4]).

The patients, too, have cooperated by voluntary submission to slight operative measures to secure material, like localized exudates, bits of muscle, lymph-nodes, fibrous nodes, synovial membrane, erythematous nodes, etc., for histologic and bacteriologic study. Cultural and other blood-studies have been made. Functional tests have been carried on. In this way a more definite knowledge has been obtained of important principles relating to (*a*) the location and the nature of the infectious organisms of the focus; (*b*) the method of systematic infection, and the resulting morbid anatomy, and (*c*) the wider application of the etiologic importance of focal infection.

THE FOCUS OF INFECTION

The focus of infection may be located anywhere in the body. The usual site is in the head, in the form of alveolar abscess, deep tonsillar or peritonsillar abscess and chronic sinusitis. Cholecystitis, acute or chronic appendicitis, submucous abscess anywhere, salpingitis, seminal vesiculitis, prostatitis, etc., are examples of the local conditions. Furthermore, secondary foci in lymph-nodes proximal to the primary focus and to systemically infected joints, mus-

1. Billings, Frank: Chronic Infectious Endocarditis, Arch. Int. Med., November, 1909, p. 409; Chronic Focal Infection as a Causative Factor in Chronic Arthritis, THE JOURNAL A. M. A., Sept. 13, 1913, p. 819; Chronic Focal Infections and Their Etiologic Relations to Arthritis and Nephritis, Arch. Int. Med., April, 1912, p. 484; Clinical Aspect and Medical Management of Arthritis Deformans, Illinois Med. Jour., 1914, xxv, 11; Focal Infection in Relation to Systemic Disease in Forchheimer Therapeusis of Internal Diseases, New York, D. Appleton Company, 1914, v, Chap. iv.

2. Davis, D. J.: Bacteriological and Experimental Observations on Focal Infection, Arch. Int. Med., April, 1912, p. 505; Chronic Streptococcus Arthritis, THE JOURNAL A. M. A., Sept. 6, 1913, p. 819.

3. Jackson, Lelia: Experimental Rheumatic Myocarditis, Jour. Infect. Dis., 1912, xi, 240; Experimental Arthritis in Rabbits, ibid., 1913, xii, 364.

4. Rosenow, E. C.: The Study of Pneumococci from Cases of Infectious Endocarditis, Jour. Infect. Dis., 1910, vii, 410; The Etiology of Articular and Muscular Rheumatism, THE JOURNAL A. M. A., April 19, 1913, p. 1223; The Production of Ulcers of the Stomach by Infections of Streptococci, ibid., Nov. 29, 1913, p. 1942; Transmutation Within the Streptococcus = Pneumococcus Group, Jour. Infect. Dis., 1914, xiv, 1; Preliminary Note on the Etiology of Arthritis Deformans, Tr. Chicago Path. Soc., 1914, ix, 115; THE JOURNAL A. M. A. April 11, 1914, p. 1146.

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cles, etc., become additional sources of continued and more general infection. "Overdentistried" teeth may cause or prolong alveolar disease. Tonsillotomy may add a sealing scar to the infected tonsillar stumps.

An investigation may reveal more than one apparent focus of infection, an important fact, inasmuch as the source of infection must be removed as the first step in treatment. Patients much reduced from long illness may suffer from alveolar or other local infection, as a secondary process. These conditions must not be mistaken for the cause of the primary systemic disease. Such secondary local infectious foci may serve as adjuvants further to prolong and intensify systemic disease.

A study of the tissues and exudates of the focus usually yields various bacteria. Of the pathogenic bacteria, streptococci, pneumococci and staphylococci are most commonly found. Gonococci may be found in infected fallopian tubes, seminal vesicles, etc. Occasionally the tubercle bacillus is found in tonsillar and peritonsillar tissues. Colon mixed infection may occur anywhere. The *Bacillus aerogenes capsulatus* is not infrequently found in pathologic tissues and exudates. A study of the streptococcus group so obtained shows, in many instances, a pathologic specificity for certain tissues when injected into rabbits or other animals. Strains obtained from cultures made from tissues and exudates of patients suffering from chronic arthritis produce arthritis in the inoculated animal; strains obtained from the focus of patients with hemorrhagic nephritis, cause nephritis in the inoculated animal; strains obtained from the focus in the patient with rheumatic fever, endocarditis and pericarditis result in pancarditis and acute arthritis in the inoculated animal, etc. (Billings,[1] Davis,[2] Jackson,[3] Rosenow[4]). Furthermore, the brilliant work of Rosenow proving the transmutability of the micro-organisms of the streptococcus-pneumococcus group has helped to a better understanding of the changing pathogenic speci-

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ficity of these bacteria. Apparently transmutation of a strain of this group may occur in the focus of infection. The oxygen supply of the tissues about the focus seems to be an important factor in the transmutation of the micro-organism. In consequence it may take on characteristics which render it pathologically specific in the infection systematically of joint-tissues or of muscles including the myocardium, or of tendons and aponeuroses or of endocardium and pericardium or of gall-bladder or of mucosa of stomach and intestine or of pancreas, or of kidney, respectively. Apparently strains with an affinity for joint-tissues and muscles, or for joint-tissues, endocardium and pericardium may develop in the primary focus. Inoculations with strains obtained from patients suffering from chronic arthritis, rheumatic fever, with endocarditis and pericarditis, myositis, peptic ulcer (surgically excised), cholecystitis (surgically operated), chronic infectious endocarditis (blood-culture), have resulted in the production of the respective lesions in the experimental animal. The interesting experiments proving the transmutation of the streptococcus-pneumococcus group by Rosenow,[4] and the positive results obtained by him in making cultures by new and ingenious methods, from tissues and exudates, in the various diseases named, have made clear many clinically obscure conditions. The transmutation of the strains in growth and specific pathologic characteristics explains, too, the varying and often contradictory results of various research workers in inoculation experimentation with animals.

METHOD OF SYSTEMIC INFECTION AND RESULTING MORBID ANATOMY

Probably the infective agent passes from the focus to other tissues through the blood-stream. Histologic examination of joint structures, heart-valves, muscles and other tissues of inoculated animals shows embolic bacterial masses in the terminal arteries. Endothelial

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proliferation at the site of the embolus closes the vessel lumen. Muscle and joint-capsule show embolism, local hemorrhage and endothelial proliferation closing the lumen of the vessels. The same process takes place locally in the submucosa of the stomach and intestine and of the fundus of the gall-bladder. Anemic necrosis and rupture into the gall-bladder is a cause of cholecystitis, acute or chronic, and if the latter, gall-stones may form. The specific streptococcus may invade vessels of the pancreas. Acute severe pancreatitis may result, or a lesser degree of infection may so diminish the blood-supply of the organ as to disturb its function, and temporary or severe glycosuria supervenes. Lessened nutrition and oxygen of the infected tissues due to the mode of infection bring about characteristic results. The anatomic changes in capsule, cartilage and bone of joints, in muscles, tendons and aponeuroses which are characteristic of chronic arthritis may be produced by ligation of some of the nutrient arteries of joints, muscles, etc. (Oxhausen[5]). Furthermore, the strains of streptococci which apparently cause chronic deforming arthritis and myositis grow best in a low oxygen tension and even grow anaerobically. The method by which they invade the tissues produces a condition of the tissues in which they thrive. The peculiar characteristics of the mode of infection, the diminished blood-supply to the tissues, the resulting morbid anatomic change and the suitable mediums for continued viability and growth of the infectious agent, explain, in part at least, the progressive nature and the difficulty of successful management of arthritis deformans.

A characteristic directly opposite of this is evident in chronic infectious endocarditis due to the *Streptococcus viridans*. Here the infection is undoubtedly

5. Oxhausen, G.: Ueber Einfache aseptische Knochen und Kurrpelenkrose, Chronditis desiccans und Arthritis deformans, Verhandl. d. deutsch. Gesellsch. f. Chir., Berlin, 1912, xlii, Part 1, p. 40, Part 2, p. 446.

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hematogenous. The scar of healed endocarditis and valvulitis is often predisposing. This infectious agent grows best in a high oxygen content. The circulating blood furnishes this in abundance. It causes an abundant vegetative growth on the valves and endocardium. In this nidus, swimming in oxygen, it multiplies, becomes immunized against the host and resists every method of treatment.

Acute rheumatic fever is of undoubted focal origin. The newer methods of bacterial culture (Rosenow[4]) have proved the presence, usually, of the infectious organism in the joint-fluid, and it may always be found in the synovial membrane and proximal lymph-nodes during the height of the disease. The strain of the streptococcus which produces these acute lesions also has an affinity for the endocardium and pericardium and often for the myocardium and some groups of the skeletal muscles. Apparently the micro-organism has other affinities. One of the clinical group (Woodyatt) called attention to an apparent thyroiditis in some of the patients suffering with acute rheumatic fever. The thyroid gland was palpably enlarged and tender on palpation. There was moderate tachycardia, tremor of fingers, unusual nervousness, excessive sweats and diminished carbohydrate tolerance. Of five patients then in wards, suffering with acute rheumatism, three showed this evidence.

Case 1.—A. X., man, aged 35, married, porter, Greek, admitted, April 1, 1914. Diagnosis: Rheumatism, acute; tonsillitis acute; thyroiditis. Complaint: March 30, 1914, illness began with soreness of throat, chilliness, pain in lumbar muscles and left heel and swelling and much pain in knees. Profuse sweats at night. Anorexia, thirst and constipation. Had rheumatic fever in 1900 and several minor attacks since then. Examination: Well-nourished; teeth good; tongue, slight whitish fur; tonsils very large, red and infected; thyroid, palpably enlarged and tender; heart and lungs normal; spleen palpable; knee-joints hypersensitive but not swollen; profuse sweating; fine tremor of fingers; temperature from 102 to 104 F.; pulse 90 to 100; blood-pressure 125 systolic; blood, reds 4,440,000, whites 13,500, hemoglobin 70 per cent.; urine scant, 1.028, acid, albumin trace, casts 0. April 2, 7 a. m.,

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glucose, 50 gm., given before breakfast. Urine voided and examined each hour. Glucose present only in specimen voided at 9 a. m. Treatment: Compound pills of rhubarb, as necessary; sodium salicylate and bicarbonate 1 gm. every three hours; oil of wintergreen and bandages applied to joints. April 18, discharged, recovered. Tonsillectomy advised and refused. April 19, readmitted for slight recrudescence. No joint-swelling and no fever. April 22, discharged; tonsillectomy refused. May 30, readmitted for tonsillectomy. Cultures from depths of tissue of excised tonsils yielded almost pure cultures of a green-producing streptococcus.

Case 2.—P. K., man, aged 25, single, laborer, Greek, admitted, April 12, 1914. Diagnosis: Rheumatism acute; endocarditis; thyroiditis; tonsillitis acute. Complaint: Acute inflammation of many joints; began nine weeks ago with sore throat, fever, sweats, etc. In Francis Willard Hospital two weeks. Apparent recovery. Recrudescence three weeks ago with sore throat, pleurodynia and polyarthritis. Denies venereal disease. Examination: Well-nourished; sweating and hypersensitive skin; tonsils large, red and infected; teeth negative; thyroid gland palpable, enlarged and lobes tender to touch; heart, left border, dulness 13 cm.; systolic murmur at mitral area; second pulmonic tone accentuated; rate 100 to 110; many points swollen, hypersensitive and painful to movement; fine tremor of hands; fever, remittent 99 to 101 F. Reds 5,260,000, whites 10,300, hemoglobin 70 per cent; blood-pressure 135 to 145 systolic; urine scant, 1.022, acid, albumin 0, sugar 0, casts 0. April 14, 50 gm. glucose given before breakfast at 7 a. m. At 8 a. m. urine = sugar 0. At 9 a. m. urine = sugar present. At 10 a. m. urine = sugar 0. Treatment: Cleansing mouth- and throat-washes; sodium salicylate and bicarbonate each 1.3 gm. every three hours; oil of wintergreen and compresses of cotton applied to joints. April 17, joints still swollen and painful. Fine tremor of fingers, systolic murmur at mitral area. April 29, convalescent. Tonsils reduced in size and no visible infection. Thyroid gland comparatively smaller and not sensitive to palpation. Systolic murmur at mitral area. May 5, discharged recovered. Tonsillectomy advised.

Case 3.—P. X., man aged 27, single, laborer, Greek, admitted, May 10, 1914. Diagnosis: Rheumatism acute; tonsillitis acute; thyroiditis. Complaint: Six days ago acute sore throat, which was followed in two days by painful swollen fingers and wrists and later all joints of extremities involved except hips and shoulders. Much sweating, headache and nervousness. Anorexia and constipation. Fever for six days. Similar attack six years ago. Denies venereal disease. Examination: well-nourished and developed. Face flushed. Skin sweating and hypersensitive. Tongue tremulous and coated, grayish-white. Teeth, sound. Tonsils large, red and infected. Thyroid, palpably enlarged and tender. Heart and lungs nor-

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mal. Polyarthritis acute of all joints of extremities excepting shoulders and hips. Temperature 100 to 102.4 F. Pulse 100 to 120. Urine, 1.028, acid, trace of albumin and a few hyaline casts. Blood: Reds 5,020,000, whites 17,800, hemoglobin 70 per cent. Blood-pressure 110 systolic. May 12, 7 a. m., given glucose, 50 gm. In three hours voided in urine glucose, 1.34 gm. Treatment: sodium salicylate and bicarbonate, each 1.3 gm. every two to four hours; oil of wintergreen and compresses of cotton applied to joints. May 28, discharged recovered. Tonsillectomy advised.

A review of the foreign literature of the last seven years shows the recognition of enlargement of the thyroid gland in acute articular rheumatism as a frequent occurrence. Vincent[6] was apparently the first to note the fact. During 1906 and 1907 he made several reports to the Sociéte médicale des hopitaux de Paris. Nov. 21, 1907, he reported that of 186 patients suffering from acute articular rheumatism he observed swelling and tenderness of the thyroid gland in 86 patients. In another communication he states that thyroiditis occurred in 66 to 68 per cent. of his patients who suffered with acute articular rheumatism. Eleven patients with acute rheumatism presented thyroid enlargement with tenderness, with acute symptoms of intoxication; tremor of fingers, tachycardia, extra cardiac murmurs and throbbing of vessels, profuse sweats, etc. Vincent observed a subsidence of the thyroid swelling, tenderness and overfunction coincidently with the convalescent stage of the rheumatism. Vincent apparently interprets the thyroid enlargement and overfunction as a reciprocal reaction of the body in defence of the rheumatic infection. He observes that in obstinate acute rheumatism with complications the thyroid may be only moderately enlarged and may quickly subside. He believes this explains the value of iodids in obstinate cases. He also thinks that the salicylates are of value in reducing this type of thy-

6. Vincent, H.: Sur la reaction thyroïdienne dans la rhumatisme aigu, et sur l'origine rhumatismale de certain cas du goitre exophthalmique, Compt. rend. Soc. de biol., 1907, lxiii, 389; Rapports de la maladie Basedow avec le rhumatisma aigu, Bull. de la Soc. méd. de Paris, 1907, xxiv, 1286; Semaine méd. March 20, 1907, p. 143; ibid., Nov. 21, 1907, p. 575; ibid., Jan. 1, 1908, p. 47; ibid, Oct. 28, 1908, p. 527.

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roiditis. He reports the continuation of the thyroid enlargement with all the phenomena of exopthalmic goiter in several patients and in a few patients with rheumatic thyroiditis subsequent atrophy of the gland with the development of scleroderma and other symptoms of hypothyroidism. Sougues[7], Albertin[8] and Weintraud[9] report similar observations of thyroid enlargement, tenderness and symptoms of hyperthyroidism in acute rheumatic fever.

None of these reporters mentions the probability of the thyroid enlargement and tenderness being due to the same rheumatic infectious agent of focal origin.

These reports and the meager personal experience noted in the cases cited aroused the interest of the clinic as to the possibility of focal infection as a cause of goiter. The following case-reports are interesting and seem to show that there is an infectious type of goiter with and without symptoms of exophthalmic goiter, which seems to be of focal origin. The rapid subsidence of the goiter and the symptoms after removal of the foci of infection in the jaws and tonsils was a surprise. Bacteriologic examination of the tissues and alveolar pus revealed mainly streptococci. Autogenous vaccines were used with one exception in all the patients. No drug treatment, with the exception of iron for one, was used.

Case 4.—Mrs. C. F., married, aged 49, U. S., admitted April 30, 1914. Diagnosis: Exophthalmic goiter; tonsillitis chronica; abscesses alveolaris. Complaint: Frequent sore throat; goiter for two years; muscular tremor for one year, much worse recently; tachycardia for more than a year; dyspnea of exertion; nervous and emotional; gradual loss of weight; lessened strength and endurance. Menopause at 47. Examination: Skin pale, pseudoscleroderma of hands, forearms and forehead; eyes normal; no lymphadenopathy; large goiter, partially cystic; heart, left border dulness 11 cm., tones

7. Souges, A.: Goitre exophthalmique et rhumatisme articulaire aigu, Semaine méd., Jan. 26, 1910, p. 47.

8. Albertin, André: Le corps thyroide et le rhumatisme articulaire aigu, Thèse de Paris, 1911; Arch. de méd. 1911, iv, 260.

9. Weintraud, W.: Der akute Gelenkrheumatismus, Spezielle Path. u. Ther. inner. Krankheit., Berlin, Kraus und Brugsch, 1913-1914, ii. Part 2, pp. 128 and 148.

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pure, rate 96 to 100; muscular tremor, fingers; many carious teeth with alveolar infection (roentgenograms); tonsils enlarged, fissured and infected; blood: reds 4,700,000, whites 7,800, hemoglobin 65 per cent.; urine, normal; blood-pressure, 130, systolic. Treatment: Tonsillectomy; extraction of all teeth; rest and plentiful food. Result: May 12, 1914, discharged much improved. Goiter diminished more than half; symptoms of hyperthyreoidea practically nil.

Case 5.—Miss J. L., aged 18, telephone operator, U. S., admitted May 2, 1914. Diagnosis: Exophthalmic goiter; tonsillitis chronica; abscesses alveolaris. Complaint: Goiter, nervousness and emotion; muscular tremor; tachycardia; dyspnea of exertion; loss of weight and strength; headache; hot flashes and profuse perspiration; tonsillitis and confinement to house for a week every winter. Duration of symptoms six years. Examination: Well-nourished and good color. No exophthalmos; tonsils large and infected; six molar teeth show alveolar infection (roentgenograms); a moderate symmetrical, firm goiter; heart normal, pulse 80 to 110; temperature subfebrile; tremor of fingers; blood, normal; urine, normal; blood-pressure 100 systolic. Treatment: tonsillectomy, extraction of teeth with infected roots, autogenous vaccination with strains of streptococci obtained from tonsils and dental canals. May 18, 1914, discharged to family physician. Goiter has disappeared. Symptoms of hyperthyreoidea much improved. June 18, 1914, the family physician reports the patient in good condition of health.

Case 6.—Miss M. W., aged 20, telephone operator, U. S., admitted May 12, 1914. Diagnosis: Exophthalmic goiter; tonsillitis chronica. Complaint: Goiter for unknown period; rapid increase in size recently; tachycardia for year or longer; dyspnea of exertion; nervous and emotional; frequent subjective flashes of heat; prominence of eyeballs for a few weeks; loss of 15 pounds in weight in last few months; frequent sore throat; tonsillotomy three years ago. Examination: General pallor; moderate exophthalmos and lagophthalmus; tonsil stumps large and infected; teeth good, some dentistry; thyroid enlarged, symmetrical and firm; heart normal size, rapid, 100 to 120, somewhat irregular, tones pure, but snappy; tremor of extended fingers; reds, 3,300,000, whites 8,300, hemoglobin 60 per cent.; blood-pressure 125 systolic; urine, normal. Treatment: Tonsillectomy; rest; hematinics and plentiful food. May 20, 1914, discharged to family physician, much improved. June 18, 1914, family physician reports the patient much improved. Goiter much diminished in size. General condition excellent.

Case 7.—Miss M. K., aged 24, telephone operator, U. S., admitted April 18, 1914. Complaint: Chronic arthritis of joints of fingers; frequent tonsillitis; goiter; occipitofrontal headache, fainting attacks and nervousness. Examination:

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Well-nourished; good color; tonsils large, fissured and infected; four lower teeth show alveolar infection (roentgenograms); swelling, soreness and stiffness of many joints of fingers; heart, lungs, urine and blood normal. No symptoms of hyperthyreoidea. Treatment: Tonsillectomy, extraction of teeth with infected roots, autogenous vaccination with streptococci (*S. viridans* and *S. hemolyticus*) obtained from tonsils and dental canals. May 10, 1914, discharged much improved. June 6, 1914, returned and reported ability to return to work. Goiter practically disappeared. June 18, 1914, patient at work. Goiter about one half original size. General condition good. Arthritis of fingers much improved.

Case 8.—Miss M. M., aged 21, telephone operator, U. S., admitted May 18, 1914. Diagnosis: Goiter; tonsillitis chronica. Complaint: Frequent sore throat, hoarseness; goiter of unknown duration, intermittent enlargement of lymph-nodes of anterior triangles of neck; nervous and emotional; lessened strength and endurance. Examination: Moderate exophthalmos and lagophthalmus; tonsils enlarged, fissured and infected; teeth, no visible infection, much dentistry; thyroid enlarged, chiefly the isthmus and right lobe; a few palpable submaxillary lymph-nodes; heart normal, 68 to 80; slight tremor of extended fingers; reds, 4,800,000, whites 10,300, hemoglobin 75 per cent.; blood-pressure 120 systolic; urine normal. Treatment: Tonsillectomy and rest. May 25, 1914, discharged to family physician much improved. June 18, 1914, family physician reports condition improved with the thyroid almost normal size.

Case 9.—Miss E. S., aged 23, U. S., admitted May 19, 1914. Diagnosis: Exophthalmic goiter; tonsillitis chronica; impacted molar teeth. Complaint: At 17 became nervous and emotional, had tachycardia, loss of weight and strength, muscular tremor, moderate goiter, sweating, diarrhea, etc. Diagnosis of exophthalmic goiter and operation advised by home physician. Instead took rest cure. Improvement. Since then invalid with periods of improvement alternating with relapses. Now has tachycardia with irregular beating; nervousness, with hot flashes, insomnia and varying emotions; muscular tremor, generalized; profuse perspiration; diarrhea; occasional nausea and vomiting; weakness; loss of weight; exophthalmos and goiter. Had acute rheumatism at 12; sore throat on rare occasions. Menses irregular. Examination: Fairly nourished. Moderate exophthalmos; teeth, no caries, impacted molars (roentgenogram); tonsils large, buried, smooth exposed surfaces; thyroid visibly and palpably enlarged; heart, left border dulness 11 cm., rate 100 to 120, rhythm, somewhat irregular, tones pure; tremor marked; temperature range 98.6 F.; carbohydrate tolerance to glucose gm. 50.0 normal; urine normal; blood-pressure 140 systolic; reds 4,500,000, whites 9,000, hemoglobin 80 per cent. Treatment: Tonsillectomy. Removal of

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impacted teeth. Rest. June 3, 1914, discharged to family physician. Goiter and symptoms of hyperthyroidea practically disappeared. June 16, 1914, a letter from the patient's sister states marked condition of general improvement. She says patient expresses surprise at the disappearance of uncomfortable sensations which had existed so long that she had thought them natural phenomena.

CASE 10.—Miss G. O'B., aged 23, telephone operator, U. S., admitted May 20, 1914. Diagnosis: Exophthalmic goiter; tonsillitis chronica; abscess alveolaris; anemia secondary. Illness began one year ago with severe tonsillitis. Soon noticed goiter with extreme nervousness, muscular tremor, tachycardia and a complete nervous collapse in March, 1914. Examination: Well-nourished; pale; nervous; marked muscular tremor; no exophthalmos; symmetrically enlarged thyroid gland; three carious teeth with alveolar infection (roentgenogram); infected faucial tonsils; subfebrile temperature; pulse 96 to 130, heart-tones normal; blood: reds 2,580,000, whites 13,600, hemoglobin 40 per cent.; blood-pressure 125 systolic; urine normal. Treatment: Tonsillectomy; extraction of teeth with alveolar infection; hematinics; rest and good food. Result: Rapid improvement in goiter and symptoms of hyperthyreoidea. June 18, 1914, patient continues to improve in a general way. Anemia less. Goiter still palpable, but symptoms of overaction of thyroid practically gone. This patient is the only one of the series of women who has not received vaccines.

No thyroid gland tissue was examined. Dr. E. C. Rosenow has recently made cultures from the deep tissues of many goiters, removed surgically in the treatment of exophthalmic goiter. Without exception he has been able to isolate and grow a streptobacillus of characteristic qualities. He is making experiments with the organism by animal inoculation and will make a report soon.

Farrant[10] has investigated the pathologic changes of the thyroid in disease. He finds that certain microorganisms and certain toxemias may cause either a chronic hyperplasia with colloid or a complete acute hyperplasia. In the acute type the *B. aerogenes capsulatus, B. diphtheriae, B. dysenteriae* (Asylum, Shiga and Flexner types), *B. anthracis, B. tuberculosis, B. mallei,* bacillus of tetanus, *Micrococcus catarrhalis,*

10. Farrant, Rupert: The Pathological Changes of the Thyroid in Disease, Brit. Med. Jour., Feb. 28, 1914, p. 470.

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Spirochaeta pallida, Plasmodium malariae, chronic nephritis, cirrhosis of liver and toxemias due to abrin, ricin and diphtheria toxin produced rapid hyperplasia. Animal inoculation and examination of animal and human thyroids were the basis of the report.

In the chronic type, the coliform bacillus (chr.) tuberculosis, chronic, Malta fever, syphilis, actinomycosis, acute poliomyelitis, rheumatic fever, scarlatina and pernicious anemia were associated with thyroid enlargement. Involution of the thyroid followed the subsidence of the systemic disease.

That Farrant should not find acute hyperplasia in rheumatic fever is probably due to the absence of clinical observation.

THE WIDER APPLICATION OF THE ETIOLOGIC IMPORTANCE OF FOCAL INFECTION

To the now well-known relation of focal infection as a chief factor in the etiology of acute rheumatism, chronic deforming arthritis, gonorrheal arthritis, malignant endocarditis, myositis, myocarditis, septicemia of various bacterial types, tuberculosis, nephritis and visceral degeneration, we may add certain infectious types of thyroiditis, with or without hyperthyroidism, pancreatitis acute and chronic, with or without resulting glycosuria, peptic gastric and duodenal ulcer and cholecystitis.

With the defenses of the body diminished by overwork, exposure to cold, dissipation, insufficient or improper food, unhygienic surroundings, injuries from former disease, (valvular scar) or trauma, the individual may suffer from acute rheumatic fever, chronic arthritis, myositis, chronic infectious endocarditis, pneumonia, ulcer of stomach, cholecystitis or pancreatitis, respectively dependent on the phase of mutation in pathogenicity, and affinity of the strain of the streptococcus-pneumococcus group in the focus of infection. These principles are important because proper management may (*a*) prevent the systemic dis-

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ease and (*b*) guide one in the proper treatment of the systemic disease. The recognition and removal of chronic foci anywhere in the body is imperative as a prevention of progressive ill health. Emphasis should be made of chronic alveolar abscess, often unrecognized by the patient. Film roentgenograms of the jaws is often the only means of recognition. A pathologic tonsil is a menace and should be wholly removed. Chronic cholecystitis and chronic appendicitis should be promptly treated surgically. Chronic sinusitis may exist for years and finally be an important factor in the development of systemic disease. Following the removal of the focal infection, adequate individual and general hygiene will improve the body defenses and health will be maintained.

The removal of the focus of infection is demanded as a fundamental principle, in the treatment of the systemic diseases especially of the chronic type. Thereafter the management must be individual, based on the character and location of the infection. The attempt to immunize the patient against the infection must be attempted by restorative measures—food, pure air, passive and active graduated exercise, hematinic and other tonics, optimistic surroundings, etc. Autogenous vaccines may be used with rational reservation.

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THE NEWER BACTERIOLOGY OF VARIOUS INFECTIONS AS DETERMINED BY SPECIAL METHODS *

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The bacteriology of most infections as worked out heretofore is largely the bacteriology of the fluids of the body and semifluid exudates. In acute infections a bacteriologic study of the fluids commonly yields trustworthy results, but in many chronic conditions the cultures are usually sterile and demonstration of bacteria in the tissues usually fails.

In this short paper I wish to describe methods for making cultures particularly from excised tissues and from the blood and other fluids in which due regard is paid to the question of oxygen pressure, particularly in the primary culture, and to detail very briefly the results obtained by their use in various infections.

PREPARATION OF THE EMULSION FROM THE TISSUES

The tissues are excised with strict aseptic precautions usually under local anesthesia and cultures made at once, a portion being reserved for microscopic study. In addition to the great care used to avoid contamination from skin or air the surface of the part used for cultures is sterilized by dipping it into boiling water, or even better, into a vigorous Bunsen flame, or seared with a hot blade, then rapidly cooled in sterile salt solution and emulsified in the specially devised sterile air-chamber or "tissue-crusher" shown in the accompanying illustrations. The amount of heat used is determined by the size of the tissue at hand. Whenever possible, pieces of tissue at least 2 to 3 cm. in diameter are used for cultures.

* From the Memorial Institute for Infectious Diseases.

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The chamber (Fig. 1) is somewhat similar to the one already described[1] except that it contains a larger mortar and a small-sized meat-chopper.[2] It consists of an air-tight tin can (19 by 23 cm.) containing a large (10 cm.) hole on one end with a flanged rim to which is tied a long-sleeved, heavy, fleece-lined canvas glove; there is a smaller side opening (3 cm.) which is plugged with cotton and a large opening (8 by 12 cm.) at the top which is covered with mica and held in place by circular wires and surgeons' adhesive plaster. The meat-chopper is held in place

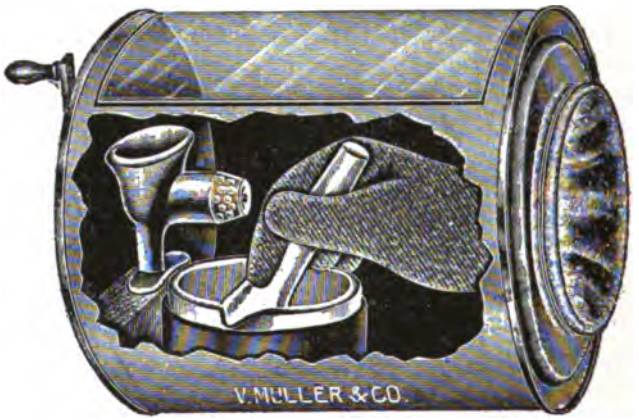

Fig. 1.—Sterile air chamber. The right hand is used inside the apparatus.

through a hole at the farther end through which the shaft extends and a hole at the bottom through which a thumb-screw fits whereby it is clamped to a wood extension, fastened to a semicircular wood board nailed to the end. On the inside is fastened a suitable-sized tin can which serves as the mortar holder. The container without the meat-chopper answers very well for small or relatively soft tissues, such as the lymph-glands in arthritis, while the one containing the

1. Rosenow: Centralbl. f. Bakteriol., Orig., 1914, lxxiv, 366.
2. The meat-chopper is an inexpensive commercial article designated the "Baby Masticator," and manufactured by the Enterprise Manufacturing Company, 176 North Dearborn Street, Chicago.

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meat-chopper is preferable for emulsifying larger and firmer tissues such as the thyroid gland, cystic ovaries and the glands in Hodgkin's disease. Sterilization is done in dry heat at 160 C. (320 F.) for one hour. For actual use the right hand and forearm are thoroughly scrubbed with soap and water and soaked in 1 : 1,000 mercuric chlorid and then introduced into the container and glove. Alcohol should not be used in sterilizing the hand because the vapors are apt to ignite with explosive violence when the side opening is flamed after removing the cotton plug; the mouth of the tube or bottle containing the tissue is flamed and held near the small opening in the side and the tissue grasped with long sterile forceps, and with the least possible exposure to the room air, inserted into the container and either cut into small pieces with the scissors or passed through the meat-chopper. Great care is exercised at all times not to move the gloved hand in or out of the container while the cotton plug is removed. After grinding the tissue in the mortar for a time, sterile quartz-sand and the emulsifying fluid, usually dextrose broth, are poured into the mortar through the side opening from thoroughly flamed test-tubes. The cotton plug is reinserted and the emulsifying process is continued. The emulsion when completed is poured into a thoroughly flamed test-tube or graduate of suitable size, inserted through the side opening.

In attempting to simplify as much as possible the emulsification of tissues and to check up the results obtained with the sterile air-chamber, the "tissue-crusher" (Fig. 2), a modification of the method used by Hirschfelder to obtain tissue juice, was devised. It consists of two close-fitting threaded metal tubes; the outer tube is fitted with an air-tight removable bottom, the inner surface being made rough, and a four-sided rim, while the inner tube is fitted with a removable disk containing numerous very small drilled holes and a handle which serves as a wrench. The inner tube is plugged with cotton and placed inside

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the other and the instrument sterilized in hot air. In order to prevent leakage the thread of the inner tube should be covered with hot sterile paraffin or petroleum oil just before using. The tissue is placed in the outer tube and the inner tube turned in the outer, using the necessary force until the tissue is crushed and expressed into the inner tube. The instrument is now

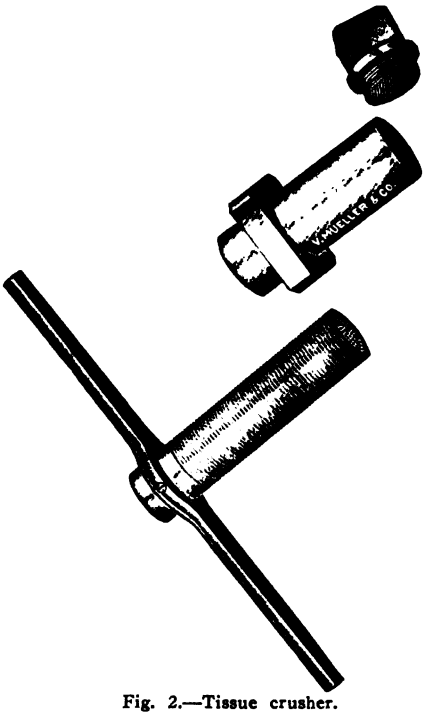

Fig. 2.—Tissue crusher.

held slantwise, the cotton plug flamed and removed, the emulsifying fluid added and the emulsion transferred to a sterile test-tube with a sterile pipet.[8]

METHOD OF PREPARING THE BLOOD-CULTURES

In order to furnish bacteria from the blood and other sources a gradient of oxygen pressure, the fol-

3. The sterile air-chamber may be made in the laboratory, while the tissue-crusher requires a well-equipped machine-shop for its construction. Both may be purchased from V. Mueller & Co., 1779 Ogden Avenue, Chicago.

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lowing method for making blood-cultures has been used with good results: From 15 to 30 c.c. of blood are withdrawn from the vein at the bend of the elbow in the usual way and decalcified, by adding it to a solution of 2 per cent. sodium citrate in sodium chlorid solution in the proportion of 5 c.c. of blood per 1 c.c. of solution. Control tests have shown that the bacteria contained in the blood from a wide range of conditions live in this solution for at least seventy-two hours. The citrate solution is kept in a tube of suitable size closed by an aluminum screw-top containing a rubber disk and sealed with paraffin. This may be used at the bedside and then sent to the laboratory for cultures in case, for some reason, it is not convenient to make the complete culture at the bedside. In my work a portion of the citrated blood has been at once planted and the remainder added by means of a sterile pipet to sterile distilled water contained in bottles which serve as centrifuge tubes, there being at least 10 parts of water to 1 part of citrated blood. This is centrifuged at once and the supernatant hemoglobin containing water is poured off or the sediment removed with a sterile pipet, and planted. The sterile water serves as a means of getting rid of the hemoglobin and the serum. Control tests with the serum after the corpuscles have separated by gravity show that in the aerobic cultures the inhibiting action of the hemoglobin is more marked than that of the serum; in fact, the serum is a desirable constituent in streptococcal cultures. Hence in suspected streptococcal infections the serum and the sediment of the dissolved corpuscles may be planted separately. In some instances the hemoglobin has been converted into methemoglobin by passing carbon monoxid (illuminating gas) through the decalcified blood by means of a sterile pipet containing a long sterile cotton plug.

THE PREPARATION OF THE CULTURES

The emulsion of the tissues or the sediment of the dehemoglobinated blood is inoculated in the way best

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suited for the particular case at hand. Shake-cultures in tall columns (10 to 20 cm.) of ascites dextrose (1 per cent.) agar and plain agar (0.5 to 0.8 per cent. acid to phenolphthalein) with or without serum have yielded the best results. The ascites fluid is collected in a sterile manner and heated on successive days to 60 C. (140 F.) for one hour or for twenty-four hours and used only after the sterility has been determined. To 9 parts of 0.5 per cent. agar, prepared from Liebig's extract of beef and Witte peptone, 1 part of ascites fluid is added with a sterile pipet after the agar is either thoroughly boiled in a bath or steamed in an Arnold sterilizer for at least fifteen minutes to drive off molecular oxygen, and cooled to 60 C. The emulsion or other material is added to the agar when cooled to 39 C. (102.2 F.) by inserting the mouth of the pipet to the bottom and forcing out its contents while the pipet is withdrawn. After the cotton plug is flamed and replaced in the test-tube the further mixing is accompanied by partially inverting the tube once or twice. Care is exercised not to blow bubbles of air through the agar.

Owing to the oxygen-consuming power of living cells the bottom of the tubes is rendered anaerobic while the top necessarily remains aerobic, and the space between represents a gradient of oxygen pressure between the two extremes. In order to bring about a still greater range of conditions in view of the consideration that the emulsion or tissue juice may be bactericidal or may favor the growth of the bacteria, only a small amount of emulsion is added to some tubes and a large amount to others. In the case of the blood-sediment or joint fluid when only a small amount is at hand, pieces of sterile rabbit or guinea-pig tissue are added to the bottom of the tube if strict anaerobic conditions are desired. A gradient of H and OH ions in the mediums, obtained by superimposing a plus 1 agar or a minus 1 agar and vice versa has also been found useful in some conditions.

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Plain serum or ascites, agar and broth, ascites-dextrose-broth in tall tubes, enriched ascites fluid, with or without sterile tissue the surface of Loeffler's serum, plain and dextrose blood-agar slants and plates, kept under aerobic and anaerobic conditions, and at times litmus-milk and ox-bile, and in Hodgkin's disease Dorset's egg mediums are also inoculated. These, while not as favorable culture mediums, have yielded positive results in isolated instances when the shake-cultures in agar were negative. The cultures are incubated at 37 C. for ten to fourteen days before they are discarded. The tubes of dextrose-agar are carefully examined for colonies in a strong light. Smears are made from the water of condensation of the Loeffler's serum and blood-agar slants, of the liquid cultures if turbid and of the sediment always, and from the bottom of the tube of agar even though no colonies are found. Colonies in the depths of the dextrose-agar are examined by breaking the tube crosswise by means of a glass cutter and a red-hot bead at the end of a glass pipet, the surface of the tube being sterilized in the flame just before breaking it. If a positive result is obtained, at least one of the subcultures is made in such a way as to reproduce as nearly as possible the conditions under which the original growth was obtained. This point is particularly important with those strains which show a preference for anaerobic conditions. Search for unknown bacteria was made in smears stained in various ways from the cut surface of the glands and various emulsions and from the depths of the cultures both by staining and with the aid of dark-field illumination.

RESULTS

By this method, which is similar to those employed by Theobald Smith and Noguchi but in which there is afforded not only aerobic and anaerobic conditions but a gradation of oxygen pressure between these two points, a gradation of H and OH ions, and a

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wide range of nutrition, positive cultures have been obtained frequently while cultures made in the usual way remained sterile.

Thus certain non-hemolyzing streptococci have been isolated from the blood repeatedly when the usual method failed or showed much fewer colonies; in leukemia this has happened as long as four months before death; in rheumatic fever during the height of the disease in 5 of 9 attempts; in peliosis rheumatica in 2 cases, and occasionally from arthritis deformans. Hemolytic streptococci were obtained from three cases of puerperal sepsis; the *Streptococcus viridans* in two cases of chronic infectious endocarditis, while the results of the usual cultures suggested the "bacteria-free stage" (Libman) of the disease. Diphtheroid-like organisms have been isolated from the blood during the febrile period in four cases of Hodgkin's disease, and the same organism from the blood as from the nodes in two of three cases of erythema nodosum in which blood-cultures were made. Diphtheroid bacilli have been isolated from the blood in four cases of severe infections resembling rheumatism; the *Bacillus aerogenes capsulatus* (*B. welchii*) from the blood in one case of bronchopneumonia, one case of acute rheumatism, and in leukemia.

Streptococci corresponding to those which I have isolated previously from the joints have been isolated from glands draining the involved joints in twelve cases and *B. welchii* alone or in conjunction with streptococci in four of twelve cases of acute articular rheumatism.

In 54 cases of arthritis deformans one or more glands draining the joints have been examined in each case. Non-hemolyzing streptococci producing usually no distinct green on blood-agar plates and often showing a marked preference for anaerobic conditions in the primary culture but otherwise resembling *Streptococcus viridans* have been isolated 32 times; staphylococcus 5 times; an organism resembling *B. mucosus*

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3 times, *Micrococcus catarrhalis* and the gonococcus once each, *B. welchii* in 14 cases, and diphtheroid bacilli in 5 cases. In 7 cases the cultures remained sterile. In both rheumatic and deforming arthritis the same organisms have been isolated simultaneously from the fluid or capsule of the joints and the excised gland.

A diphtheroid bacillus showing a wide range of preference for oxygen in the different cases has been cultivated in all of some 40-odd cases of Hodgkin's disease; a staphylococcus in 17; *Streptococcus viridans* in 7; *B. welchii* in 14, and an unidentified Gram-negative motile bacillus in 6 cases.

A non-hemolyzing, sometimes green-producing (blood-agar) streptococcus has been obtained from the depth of the tissue in 16 of 21 chronic indurated duodenal and gastric ulcers, and from the small glands adjacent to the ulcer in 4 of 5 cases. A staphylococcus-like organism was present usually in smaller numbers in 16; *Staphylococcus aureus* only once. The base of the ulcers was either entirely sterile or contained only a small number of bacteria and yeast-cells. The number of colonies of streptococci was roughly proportionate to the gross or microscopic evidence of inflammation. Only one perforating ulcer was examined and this showed the largest number of colonies of streptococci. The negative results obtained were in ulcers which seemed to be practically healed. *B. welchii* was isolated from the ulcers in 6 cases and from the adjacent glands in 3. Three ulcers showed diphtheroid bacilli, 4 yeast-cells, and in a number there were found a few colonies of a large Gram-positive aerobic bacillus, probably belonging to the *subtilis* group. The colon bacillus was found only once in the simple ulcers excised at operation, but was present in large numbers in one examined shortly after death and in small numbers in two out of three ulcers the seat of carcinoma.

Streptococci quite similar to those from the ulcers have been isolated in pure culture from the excised

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tissue of the gall-bladder in cholecystitis in one case and from the center of gall-stones in 4 of 7 cases. *B. welchii* and *B. coli* were found together with the streptococcus in the gall-stones in one case and a bacillus resembling closely the typhoid bacillus in another.

A polymorphous, sometimes clubbed, diplobacillus was obtained in pure culture from excised nodes in each of 7 cases of erythema nodosum; from a cervical lymph-gland draining an infected tonsil in one case and in mixture from the focus of infection (tonsil and superficial ulcer on anterior pillar) in 2 cases of erythema nodosum.

An anaerobic Gram-positive diplobacillus-like organism has been isolated from the thyroid gland removed at operation in 25 out of 32 cases of goiter (mostly exophthalmic goiter) in man, from the blood on two occasions in a severe case of exophthalmic goiter, and in conjunction with Dr. Moon, in 8 of 12 dogs having goiter. We failed to obtain the organism from the gland in six of seven dogs showing apparently normal-sized thyroid glands, while one showed a few colonies. *B. welchii* was found in all but 6 of the thyroid glands examined. Three of these were normal glands in dogs. A staphylococcus which usually produces hemolysis on blood-agar and grows unusually well anaerobically was found in most of the goiters in those from both man and dog. It is as yet impossible to state whether or not this coccus comes from the skin, although it perhaps does not. Non-hemolyzing streptococci have been isolated in 3 goiters from man and in 2 goiters from dogs.

Cystic ovaries from 25 patients have been examined by this method. Streptococci, often good green-producing, have been found in pure culture in 14, in some instances, both from the cyst fluid and the emulsified tissues; but the cyst content is usually sterile. A partially anaerobic diplobacillus resembling quite

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closely the organism from the thyroid gland has been found in 4; staphylococci in small numbers in 3; *B. welchii* in all but 5 cases.

SIGNIFICANCE OF THE FINDINGS

The common localization and lesions produced on intravenous injection of streptococci soon after isolation from acute rheumatism, from arthritis deformans, from ulcer of the stomach and from the tissue of the gall-bladder in cholecystitis and the center of gall-stones, together with other facts, suggests strongly that they are not secondary invaders but the important etiologic factor in each of these conditions because the strains from rheumatism commonly produce arthritis, endocarditis, myocarditis and pericarditis; the strains from arthritis deformans, arthritis and myositis but rarely endocarditis or pericarditis; the strains from the depths of ulcers of the stomach often show a striking affinity for the mucous membrane of the stomach and duodenum (dogs and rabbits); while those from the gall-bladder and the center of gall-stones commonly produce cholecystitis. The bacillus isolated from erythema nodosum when injected as isolated showed a marked affinity for the subcutaneous tissue in dogs, rabbits and guinea-pigs, producing localized hemorrhages followed by infiltration resembling the nodes seen in man, the lesions often being symmetrically placed usually near a relatively large blood-vessel. On artificial cultivation and on animal passage the strains lost this peculiar property. In both instances the organism tended to become a streptococcus and on passage it acquired an affinity for the joints, fascia, muscles and endocardium. This fact would seem to afford an explanation of the common occurrence of arthritis and sometimes endocarditis in erythema nodosum and allied conditions.

The almost constant presence of diphtheroid organisms in the glands and their demonstration in the blood in Hodgkin's disease in conjunction with the results

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of experiments on monkeys by Bunting and Yates and by Negri and Mieremet, and the good results obtained in some cases by the use of autogenous vaccines suggest strongly that these organisms play at least a prominent rôle in this disease; but the fact that other organisms are commonly found also and that diphtheroid bacilli indistinguishable from some of the strains from Hodgkin's disease are found in many other conditions compels one to wait for more experimental evidence before concluding that these bacilli are the real cause of Hodgkin's disease.

The etiologic rôle of infection in goiter is becoming more apparent; enlargement of the thyroid gland has been noted in various infections, particularly in rheumatism; and the peculiar distribution of endemic goiter, and other clinical facts, suggest that the cause of simple and exophthalmic goiter may be due to an infection. The symptoms and the enlargement of the gland, however, have usually been considered toxic in nature and not due to localization of the bacteria in the gland. No one, as far as I can learn, has isolated an organism from the thyroid in a series of cases. The fact that the same organism has been isolated from goiters in both dogs and man, and in the latter apparently in proportion to the degree of symptoms and from the blood, the absence of this organism in normal thyroid glands in dogs, the fact that it lives longer in the thyroid gland than in the kidney and other tissues of dogs following intravenous injection, and that goiter has appeared in two dogs after intravenous injection of this organism, suggest that goiter may be due not only to toxins produced in other regions of the body but to an actual localization in the gland of bacteria. Studies of the chief organism found show that it is probably closely related to the streptococcus group and this may explain why thyroid enlargement is observed commonly in rheumatism and in cases having foci of infection in which the predominating flora is streptococcal.

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The significance of the findings of the streptococcus in cystic ovaries is not yet clear. Further experiments on animals are necessary and the immunologic reactions in the various conditions, particularly in goiter and cystic ovaries, need to be worked out before definite conclusions can be drawn. It may be that the organisms isolated are merely secondary invaders. The rather frequent occurrence of diphtheroid-like organisms in the tissues and blood during life is, I believe, significant. They are probably not wholly secondary or harmless invaders.

Altogether the *B. welchii,* or an organism closely related, has been isolated from various tissues in man 103 times and from the blood or joint fluids six times. It has frequently been found in various tissues, such as the thyroid, muscle and kidney of dogs and occasionally in livers of rabbits and guinea-pigs. On account of this surprising finding and because the organism is an anaerobe and spore-bearing, every possible source, especially the serum and ascitic fluids, other than the tissue inoculated has been excluded by control-tests. The common presence of this organism in the tissues of man and the dog (carnivorous animals) and its absence in the rabbit and guinea-pig (herbivorous animals) is, I believe, of significance. It exists in the tissues probably chiefly in the spore form and the growth usually does not result except when the oxygen pressure has reached a certain grade. The fact that the strains grow readily at a certain grade of oxygen pressure without production of gas and that they produce the characteristic growth with gas formation only under strict anaerobic conditions suggest that under special circumstances (a lowered oxygen pressure, increased virulence or growth in symbiosis with other bacteria perhaps) *B. welchii* may not be an entirely harmless invader.

Finally, whatever the ultimate significance of these findings may prove to be, the common isolation of bacteria from tissues which have been considered

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sterile is of definite importance, lends support to the contentions of Adami and others that certain ill-understood conditions are due to a low-grade infection and not merely intoxication and calls for an extensive study of the whole question by this or similar methods.

I wish to express my very great appreciation to the numerous physicians, particularly Dr. Billings, who have supplied me with material. The more complete reports are to appear in the *Journal of Infectious Diseases.*

629 South Wood Street.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. BILLINGS AND ROSENOW

Dr. William S. Thayer, Baltimore: There has been no one circumstance in the last fifteen years that has so changed the aspect of the practice of medicine as the recognition of the influence of local foci of infection on the production and course of a variety of general processes of previously uncertain etiology. In the discussion on cardiac disease, Dr. Cabot, in his classification, referred to the "rheumatic" cases, stating that although the term was rough and general, it yet covered those infections which are commonly associated with arthritis as well as cardiac disease. It is well to emphasize this association. When one meets to-day a mitral stenosis or insufficiency he proceeds in a very different way from that in which he did twenty years ago. One's first thought now should be to search for a focus of chronic infection by the removal of which the probability of progression of the malady may be greatly reduced. The proportion of cases of valvular disease of uncertain origin that show old chronic affections of sinuses, of teeth, especially of the tonsils, is very large. I would emphasize also that in tonsilar operations it is most important that the operation be complete. In a very large number of patients who come to me with the statement that their tonsils have been removed, it is easy to demonstrate that most of the lower pole of the tonsil is still present, the crypts often sealed by cicatricial tissue and more dangerous perhaps than before operation. Even in the hands of men whose technic is very good it is not uncommon to see in young people a hyperplasia of small islands of lymphoid tissue which remained after operation. These little islands may later be infected and give rise to all the symptoms formerly experienced.

Dr. A. C. Griffith, Kansas City, Mo.: It has been my good fortune since the discovery of the diphtheroid bacilli to see a few cases of Hodgkin's disease. One case in par-

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ticular occurred in an elderly lady who had been suffering for six or seven years with glandular enlargement. We removed one of these glands and developed the diphtheroid bacillus; also a coccus. Dr. Rosenow has described their clinical characteristics. These organisms are mostly of the aerobic type. The patient was put on autogenous vaccines made from the growth of the organism. The treatment was given in gradually increasing doses until the swelling of the glands began to disappear and the patient was doing nicely. She, however, was persuaded to take up Christian Science. Two weeks later I was called in when she was dying from overinfection or intoxication as a result of the activity of the glands. Necropsy showed that the changes in the glands were those characteristic of Hodgkin's disease; there was the degeneration and softening in the center and the outer harder portion. We used the vaccines three hundred millions to the cubic centimeter. I started in with 0.5 c.c. and increased the dose to 2 c.c. I gave first a dose every three or four days and toward the last 2 c.c. every other day, and the glands were disappearing when the patient left me to follow one of the cults.

Dr. Frank Smithies, Chicago: In the study of the histories of nearly ten thousand cases of gastro-intestinal trouble I have been struck by the fact that aggravations of the disturbances were quite common in the spring and the fall. It will be especially noted that this happens in the case of peptic ulcer. It will also be recalled that these seasons of the year include the periods during which epidemic infectious diseases are most prevalent. In view of Dr. Rosenow's investigations, infection of the gastric mucosa by microorganisms might occur at these periods during the course of the disease. In the case of ulcers already existing, reinfection may occur and the process be lighted up. The acid reaction of the stomach is no criterion of its bacterial cleanliness. I have shown this by my study of the findings in more than 7,000 consecutive test-meals. In the majority of the gastric-ulcer cases, there is a possibility of finding foci of infection elsewhere. Studying 1,500 peptic ulcers, I find that in more than 60 per cent. coincident or earlier infection of the gall-bladder or appendix could be noted. In cases of cholecystitis, with or without stones, there was pancreatitis in 12.5 per cent., and in common-duct obstruction, pancreatitis was noted in more than 28 per cent. of instances. It should be emphasized that cleaning up a local focus, as in the mouth, does not guarantee that patients will recover from damage that has already been done in the extensive area of the gastro-intestinal tract.

Dr. E. Libman, New York: The occurrence of exacerbations in cases of duodenal ulcer following so-called colds has been particularly emphasized by Hershell of London. In

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trying to establish a diagnosis between duodenal ulcer and cases of functional disturbance a history of such occurrence is of value. I was interested in Dr. Rosenow's statement that he is not willing definitely to accept the organism described in connection with Hodgkin's disease as being the cause of the disease. Dr. Celler has made a study of a number of cases of various forms of diseases of lymph-nodes and has found the bacillus not only in cases of Hodgkin's disease, but also in other diseases of the lymph-nodes, and particularly in two cases of typical tuberculosis. Apart from that, the *Streptococcus viridans* has been found in lymph-nodes in cases of Hodgkin's disease as well as in other lymph-nodes. Complement-fixation tests made by Dr. Olitsky in cases of Hodgkin's disease have proved to be absolutely negative in all instances. These findings lead us to be careful before accepting the organism as being the etiologic factor in the disease and make us keep in mind the question of latent microbism. There is no doubt that Dr. Rosenow has produced definite mutations in the streptococcus-pneumococcus group. As regards Dr. Rosenow's statement that the organisms from a certain type of infection cause, at least for a time, the same lesions in animals as in man, some work done by Drs. Rothschild and Thalhimer indicate that exceptions occur. They succeeded in 50 per cent. of the inoculated animals, in producing arthritis with recently inoculated strains obtained from cases of subacute endocarditis in man. Pericarditis has been found in animals inoculated with the same organisms and this is a very unusual phenomenon in the disease from which the organisms are obtained.

Dr. James M. Anders, Philadelphia: These two papers rivet the attention of the profession especially on the head as the seat of infective foci. It has long been well understood that in the case of acute miliary tuberculosis invariably an old focus exists somewhere in the body, most frequently in the lungs, from which the tubercle bacilli come. These papers emphasize the importance of a careful inspection of the mouth and throat as a part of our routine examinations of patients. If foci of inflammation are found there, they should, of course, be energetically attacked without delay. It is important to recollect that if removal of such focal infections fail to bring about a cure of the condition from which the patient may be suffering, it is not evidence to the contrary, but means, as pointed out by Dr. Billings, that hematogenous metastasis has already taken place. The American Medical Association has its Section on Stomatology, and it would be entirely proper, it seems to me, for the Section on Practice of Medicine to urge, through the House of Delegates the establishment of chairs of Stomatology in our medical colleges.

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Dr. De Lancey Rochester, Buffalo, N. Y.: I wish to speak of focal infections especially of the teeth and tonsils. In three cases having teeth infections accompanied by endocarditis in which there were no manifest symptoms in the mouth, but in which the Roentgen ray showed an abscess at the roots of the teeth, when the abscess was removed the symptoms subsided and the patients improved clinically. The organism found was the ordinary streptococcus pyogenes. I have had four cases which have impressed on me the importance of having the tonsils completely removed in cases of infection. The danger of an incomplete operation is illustrated in one case in which the toxic process had gone too far before the trouble was recognized. The patient was a woman who gave a history of rheumatism, multiple arthritis and endocarditis which had been treated in the hospital for two weeks. She improved under the salicylates and got up. Later she had a recurrence, ushered in with a temperature of 104.5 F. and her pulse was uncountable. She gave a history of having had a tonsil operation ten years before. There was also a history of sore throat and an exudate over the tonsils. The condition of the patient was so serious that she could not be operated on. She died of severe systemic toxemia, in all probability due to infection from the tonsils.

Dr. Alfred Stengel, Philadelphia: Dr. Rosenow's statement with regard to the cause or the part played by the organism in Hodgkin's disease was very conservative. He said that we are not sure of the relation of the diphtheroid organism to Hodgkin's disease, but it seems to me that we are sure that this organism is the specific organism of Hodgkin's disease. I have only four cases of such infection to report: one of endothelioma; chronic simple inflammation of the glands; one of lymphoid enlargement in a patient with rheumatoid arthritis, and lastly another rheumatoid case not easily classified.

Dr. J. Birney Guthrie, New Orleans: Has Dr. Rosenow applied his technic in finding the cause of the short fevers of obscure origin in children, which are accompanied by lymphatic enlargement—the so-called glandular fevers? These symptoms of unexplained fever and lymphatic enlargement are quite common in children and it would be interesting to have this method applied to their investigation.

Dr. Harvey D. Wood, Fayetteville, Ark.: Owing to the rapid progress that has been made in our knowledge of the cause of inflammation and infection, I believe the time has come when the definition of the termination "itis" should be made to include infection as well as inflammation. Since listening to Dr. Billings' paper and the following discussion I have been more than ever fully impressed with the need

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of a more comprehensive definition of this termination. The phenomena of seasonal recurrences and exacerbations of ulcer, due to infection, have been so clearly set forth in this discussion that it gives us a better understanding of many pathologic processes. The infection that comes from the bite of the infected bedbug is now thought by some, who are doing special work on this line, to be the cause of pellagra. This disease has its period of exacerbation in the springtime, when this pestiferous insect begins to get busy. Should this prediction prove to be the true source of the pathology of this disease, there are many persons whose minds will be relieved from the fear of having this malady.

Dr. Frank Billings, Chicago: In our group of workers we know that Dr. Rosenow is dependable. He has an opportunity to study disease clinically. The diphtheroid bacillus has been successfully cultivated from the enlarged lymph-nodes of about forty, and from the blood of five patients with Hodgkin's disease. These five had fever. The histology of the glandular tissues varied from typical Hodgkin's to simple lymphocytomas, lymphosarcoma and tuberculosis. In one lymphosarcoma the organism could not be cultivated. Many of these patients have received the autogenous vaccine subcutaneously in the dosage of 10,000,000 to 1,500,000,000, usually repeated once a week. Two have received the vaccine in large doses intravenously. Used subcutaneously there is no recognizable general reaction. Intravenously, general reaction has been noted; fever, rapid pulse, general discomfort, headache, etc. Practically all patients have also been treated with efficient roentgenization. In the chronic non-febrile cases the vaccines and roentgenotherapy seem to produce better results than the Roentgen ray alone. We are now preparing a report on the series of patients. Dr. L. Hektoen will report the histopathology of the glands, Dr. Rosenow will give the bacteriology and I shall prepare the clinical data. We are now attempting to immunize a horse with mixed strains of the diphtheroid bacillus. If successful we shall add the serum to the treatment.

Dr. E. C. Rosenow, Chicago: One word as to the importance of foci of infection other than those of the mouth. I recently saw a patient in Dr. Billings' service who had a rheumatic endocarditis, pericarditis, etc., which apparently was the result of an infected ingrowing toe-nail. The toe was operated on, the streptococcus isolated and the disease reproduced in dogs and rabbits. Another patient had a severe rheumatism including pericarditis and endocarditis which began ten days after a crushing injury of the thumb. Again the disease was reproduced with the streptococcus isolated from the wound on the thumb. I am sorry that I am not prepared to say what the cultures of the glands show in the short fevers in children with glandular enlarge-

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ment. I believe that the glands in these cases contain bacteria which are the cause of the disease. Streptococci were isolated from the glands in seven of the cases of Hodgkin's disease. It is quite well known that ulcers heal more quickly in the cardiac end of the stomach than in the pyloric end or duodenum. This is generally believed to be due to mechanical causes, but if streptococci play a rôle in the etiology of ulcer, as seems likely, why might not this be due in part to a greater bactericidal power of the mucous membrane of the former because acid-secreting, than that of the pylorus and duodenum in which no acid cells are present? The infectious nature of ulcer would best explain the seasonal exacerbations and the recurrences which come without known cause, the recurrences taking place when the immunity of the blood from a previous attack has disappeared. The most important factor in the management of ulcer of the stomach—the recognition and removal of various foci of infection—has been overlooked in the past. Proper regard of this point should reduce the incidence, percentage of recurrences and earlier healing of ulcer of the stomach and duodenum.

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THE LATE MANIFESTATIONS OF INHERITED SYPHILIS

WITH ESPECIAL REFERENCE TO ARTERIAL DISEASE

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Strictly speaking there is no inherited syphilis. Congenital syphilis better describes the condition, but even this does not convey the idea that the condition is in reality an acquired antenatal infection, the spirochetes being present in the placental blood. Many years of usage, however, have given these terms a permanent place in medical nomenclature.

It has long been known that syphilis is the most common cause of fetal death and that many of the children who do not succumb to its effects during the first few months carry its mark throughout life. But so vague and misleading are the symptoms of syphilis hereditaria tarda that except for the cases of interstitial keratitis, the diagnosis is one of the most uncommon in medicine. Yet the number of persons with an inherited infection perhaps equals those with acquired syphilis. The recognition of this condition is made more difficult by the frequent absence of the stigma we commonly associate with congenital syphilis. The key to the puzzle often lies in the family history. In addition to the points usually covered, inquiry should always be made as to the health of all living members. In no other class of patients does this part of the anamnesis attain such great importance. The history of paternal death from apoplexy or sudden heart-failure in early life means syphilis in the vast majority of cases, as does death from paresis, tabes or aneu-

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rysm, and in an obscure case we will do well to consider the possibility of congenital lues in our patient. Yet parental longevity is no guarantee against syphilis, as the grandmother of one of my patients was known to have been infected by her husband in middle life, and, though she subsequently gave birth to two imbecile children and had leg ulcers till the time of her death, she lived to be 93. I have recently obtained a strongly positive luetin test in a man of 91 who is recovering from a slight stroke of apoplexy. He had what was probably an urethral chancre fifty years ago.

Several times the first clue came from the statement that the mother had had several miscarriages and perhaps lost a number of infants in early life. In one instance it was ten years before it occurred to me that a frail little unmarried woman who was always ailing and seemed to have no resistance, might have had a congenital infection. She had a perfectly compensated mitral stenosis and aortic regurgitation, and gave a vague history of rheumatism when a child. Her mother had died suddenly at 46 and her father had also died young. Though there had been a large family, she was the only one living. Her luetin test was positive, one Wassermann weakly positive, and the improvement in her general condition after neosalvarsan and mercury was very gratifying. As she explained it she "felt like a real woman."

Fournier[1] states that congenital syphilis in a parent has the same effect on the fetus and infant that acquired syphilis has. He detected signs of active lues in 14 per cent. of the children of 116 families in which one parent had congenital syphilis. Of eighty-one pregnancies occurring in families in which one parent was an heredosyphilitic, death resulted before or soon after birth in 59 per cent.

As most of the statistics concerning congenital syphilis were made before the day of the Wassermann and luetin tests, it seemed desirable to apply them to

1. Fournier: Treatment and Prophylaxis of Syphilis, New York, Rebman Company, 1907.

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a series of persons whose parents were either clinically syphilitic or had a positive Wassermann or luetin reaction.[2] Many of the cases belonged to the latter group and in a number of instances the parents were not conscious of ever having had lues. Tabes, paresis and aortic disease were considered as evidence of syphilis. A few observers have reported the results of the Wassermann test on whole families, but, so far as I know, the luetin test has not been used in conjunction with the Wassermann in any such series.

Luetin is the name given by Dr. Noguchi of the Rockefeller Institute to an emulsion of killed spirochetes prepared by him, which, when injected between the layers of the skin, produces a reaction in syphilis which is specific for the disease. Dr. Noguchi very kindly supplied the luetin for the tests.

In all, 68 persons—adults and children—were tested from 32 families. It so happened that no infants were included.

TABLE OF RESULTS OF TESTS IN THIRTY-TWO FAMILIES

	No. of Individuals	No. Wassermann Tests	Per Cent. Wassermann Positive	No. Luetin Tests	Per Cent. Luetin Positive
Irrespective of health	68	52	17	68	59
Apparently healthy (robust) ...	33	22	0	33	39
Those with obvious ailment*	35	30	43	35	77
* Either the Wassermann or luetin was positive in				31	88

It is seen from the accompanying table that 56 per cent., irrespective of their condition, had a positive luetin test and but 17 per cent. a positive Wassermann. Thirty-three appeared perfectly healthy and of this number 39 per cent. gave a positive luetin but in none was the Wassermann positive. The remaining thirty-five deviated more or less from our standards of health, but only a small minority would be classed with what

2. Most of the Wassermanns were made at the laboratory of the State Board of Health under the direction of Professor Conn of Wesleyan University. I am indebted to Dr. Jessie W. Fisher for making a number of tests for me at the State Hospital for the Insane in Middletown, and to Dr. John A. Fordyce of New York for several tests made in his laboratory. A few were also made by Dr. Henry C. Russ of this city.

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we commonly think as congenital syphilis. For instance, the "Hutchinson triad" of deafness, interstitial keratitis and peg-shaped teeth, was uncommon, as were enlarged epitrochlear glands. Several had the "olympic forehead" but the typical saddle-shaped nose was not seen. Anemia, malnutrition, extreme nervousness and disease of the aorta and its valves were the most common diagnoses. Very severe headache was the chief complaint in a number of instances, while others had vague pains, called "rheumatism." One patient, a man of 47, had an angioneural arthritis as described by Solis-Cohen,[3] another had Raynaud's disease. Of this group, 43 per cent. gave a positive Wassermann and 77 per cent. a positive luetin. In this latter group, however, there were four whose Wassermann reaction was strongly positive with a negative luetin test. If these be added to the twenty-seven in whom the luetin was positive, we find that 88 per cent. gave either a positive luetin or Wassermann reaction.

Six children from three families in which one or both parents had inherited syphilis were studied. Three, or 50 per cent., had a positive luetin test. Two grown sons in good health did not react to either test. One rather frail boy had a negative luetin and a doubtful Wassermann. Of the other three, one, an exceedingly nervous girl of 16 who had chorioidal scars in one eye, gave a positive luetin and a doubtful Wassermann. Her sister with dactylitis had a positive luetin and a weakly positive Wassermann. They were both premature babies, as were two others of that family. The third, a delicate boy with pyrexia is of especial interest.

Tuberculosis had been diagnosed in this boy, aged 9, because of a more or less constant pyrexia which was associated with weakness and anorexia. When he first came under my observation he showed signs suggestive of enlarged bronchial glands, and I concurred in the diagnosis. The heart was free from murmurs but showed a slight sinus arhythmia. Shortly thereafter the father (Mr. X) came to

3. Solis-Cohen: Am. Jour. Med. Sc., 1914, cxlvii, 228.

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me for an examination of his lungs because an eminent laryngologist in New York strongly suspected laryngeal tuberculosis. No evidence of any pulmonary lesion was found. As the patient, who was a man of intelligence, not only denied any venereal disease, but stated he had never had intercourse with any one save his wife, syphilis seemed out of the question. Moreover, laryngologically, it was not the picture of syphilis. He stated that his father had died of paralysis at 56, but further questioning elicited the fact that he had had his first stroke of apoplexy when he was 42. (One may assume that apoplexy before 50 usually means syphilis, between 50 and 60 frequently syphilis and after 60 possibly syphilis.) His father also developed delusions—accused his wife of infidelity, etc.—that were suggestive

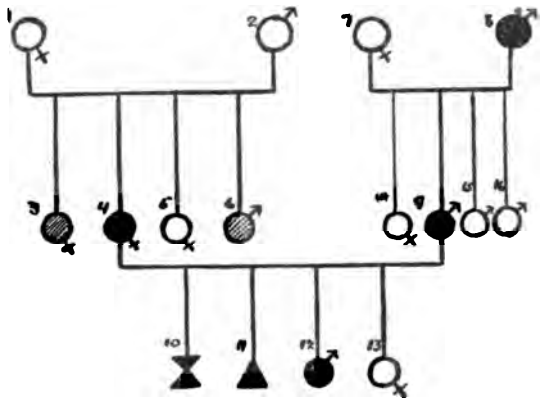

Chart 1.—Pedigree of family of Mr. X. In this and the following charts the circles indicate individuals, sex being shown by the regular signs (♂ for male, ♀ for female). Black circles represent persons known to have syphilis; shaded circles denote suspicious history or physical signs; black triangles indicate miscarriages, and double triangles stillbirths. 1 and 2. Living; not examined; said to be in good health. 3. Living, aged 42; malaria (?) as child; severe ulceration of throat; totally deaf. 4. Living, aged 40; vere severe headaches all of life; Raynaud's disease; Wassermann —; luetin +. 5. Living, aged 38; many operations in girlhood for some "bone disease." 6. Living, aged 25; "Olympic head"; deafness about twentieth year; interstitial keratitis. 7. Died, aged 54; tumor of kidney. 8. Apoplexy at 42; paresis (?). 9. Living, aged 39; exceedingly nervous; laryngeal lesion improved by neosalvarsan and mercury; luetin +. 10. Stillbirth. 11. Miscarriage. 12. Living, aged 9; very frail; Wassermann ±; luetin +. 13. Living, aged 2; very prominent forehead; not tested. 14, 15 and 16. Not examined; said to be in good health.

of paresis. I thereupon gave Mr. X. the luetin test and a positive reaction resulted. Under neosalvarsan and mercury injections Mr. X.'s throat improved markedly. As his father possibly had paresis it is of interest that he has always been exceedingly nervous, once having to give up business because of nervous prostration. His little son gave

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a negative reaction to the intradermic tuberculin test, but reacted strongly to luetin.

Mr. X.'s wife gave the following interesting history. Her parents are living and said to be well. She was never strong as a child and has always been subject to severe headaches which were not relieved by glasses. Her teeth were very poor. About six years ago she began to have typical attacks of Raynaud's disease. Her first pregnancy resulted in a still-born child at term, the second one miscarried at the third month, the next, the delicate boy whose history has been given, and the fourth a girl not as yet tested, has an "Olympic" forehead. Her family history contains the following noteworthy points.

Her oldest sister became deaf in early womanhood and had a severe ulceration of the throat of unknown origin. As a child she had some indefinite sickness, accompanied by pyrexia, which was called "malaria." Another sister had a number of operations for bone-disease thought to be tuberculous. A brother, aged 25, who has very marked frontal eminences, became deaf in his late teens, and at about 20 it is stated that a "film" appeared over both eyes and though he was almost blind for a time, he recovered under treatment. Mrs. X. gave a negative Wassermann reaction but a very positive luetin test. It would seem that both Mr. and Mrs. X. were heredosyphilitics.

The next family resembles the preceding one in several particulars.

Mr. Z., a man of 36, who knew of no venereal infection, complained of "weak feelings," pressure in his head, and of great nervous exhaustion. He had "doctored for uric acid" a great deal. Ten years previous to being seen he had to stop work for nearly a year, because he could not think clearly and easily. He was very easily exhausted. Once he had a weak spell and had to be taken to a hotel. He was fearful his heart was weak. He occasionally had a catch in the left side, and, as he expressed it, was "easily wilted." Eighteen months previously he had to stop work for three months. He found his duties, which were those of office work, arduous because of difficulty in concentrating. When the weak spells came on, the left side of the body felt numb and he experienced a drawing sensation to the left side. For the previous four years much of the time he has had intense headaches which are worse at night. His head always felt bad on waking in the morning. He also suffered much from hot flashes. The man was well nourished and looked the picture of health. The physical examination was absolutely negative, and from a purely clinical point of view was a case of neurasthenia. In his family history, however, it was found

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that his father, who died at the age of 68, had had locomotor ataxia for a number of years, and before his death two strokes of apoplexy. An elder brother has been extremely nervous and for that reason had to give up his business. A younger brother had very severe headaches for a number of years in early life, occasionally so intense that he would fall to the ground. His mother had had two miscarriages. A number of Wassermann tests by two different laboratories were negative, but the luetin test was strongly positive before giving treatment and also at present. Following several injections of neosalvarsan and mercury he was completely relieved of all his symptoms. Unfortunately, the spinal fluid was not examined.

Mrs. Z. has been very delicate since girlhood. Though ambitious, her strength fails her and she has always been

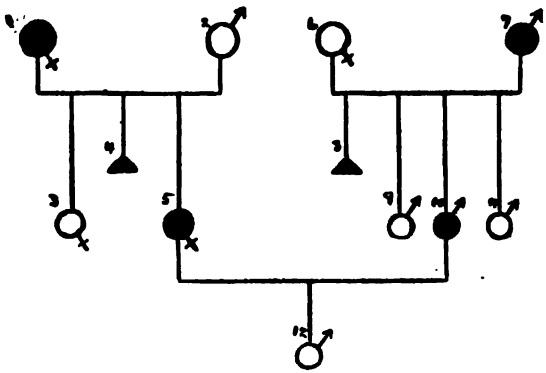

Chart 2.—Pedigree of family of Mr. Z. 1. Living, aged 64; hypertension; several slight strokes of apoplexy; luetin +. 2. Living, aged 70; angina pectoris; luetin —. 3. Living, aged 44; apparently well; Wassermann —; luetin —. 4. Living, aged 38; frail since girlhood; pulmonary tuberculosis; Wassermann —; luetin +. 6. Living, aged 70; good health. 7. Apoplexy at 68; had had tabes for several years. 8. Miscarriage. 9. Living, aged about 40; extremely nervous; not examined. 10. Living, aged 36; neurasthenia with severe headaches; Wassermann —; luetin +. 11. Living, aged 18; pleurisy; Wassermann —; luetin —. 12. Living, very robust, aged 14; Wassermann —; luetin —.

a "weakling," but without obvious cause. Recently a very slight apical tuberculosis was discovered, but it hardly seemed enough to account for her marked loss of vitality. Nor did a course of tuberculin treatment benefit her. Two different serologists reported the Wassermann negative but the luetin was very strong. Her father has had angina for several years and her mother, though apparently well, has hypertension and has had several strokes of apoplexy. Mrs. Z.'s mother gave a positive luetin test, but in her husband it was negative. Mr. and Mrs. Z. have one boy aged 14 who is healthy and in whom both tests were negative.

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One of the most common effects of congenital syphilis is its interference with the normal development of some particular part of the body. It may be mental or physical. It may involve one organ or a group of organs. There are cases on record of the complete transformation of a thoroughly incorrigible and vicious child by specific treatment. In addition to this, Fournier calls attention to what he very happily terms the "fragility of the system" as evinced by the proneness to diseases of all sorts, but especially tuberculosis. This is a very important group, of which Mrs. Z just referred to is an excellent example. "They frequently die," Fournier says, "at an early age 'of nothing at all,' so to speak, without any definite disease, and in many of such cases the most careful autopsy does not reveal the cause."

In some of my patients the dystrophies which Fournier mentions were evident. In one family of which the father had acquired syphilis before marriage, each of two daughters had a short arm and a son with interstitial keratitis stammered bad and had bilateral hernia. In another family in which the father, a congenital syphilitic, had angioneural arthritis, a son was a cryptorchid and a daughter suffered from vasomotor disturbances of the hands and feet similar to those of her father.

Hubner was the first to direct universal attention to the study of the relationship of specific disease to the blood-vessels, and to-day it is generally appreciated that the majority of the clinical symptoms of syphilis are caused by changes in the arteries with their secondary consequences.

It has long been known that acquired syphilis attacks the aortic arch with great frequency, but very little has been written concerning the rôle played by congenital syphilis in this respect. Rebaudi[4] found changes in the aorta similar to those observed in

4. Rebaudi: Monatschr. f. Geburtsh. u. Gynäk., 1912, xxxv, 681; abstr., The Journal A. M. A., Aug. 10, 1912, p. 490.

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acquired syphilis in thirteen out of seventeen still-born children. Roch and Weisner[5] found similar changes in 59 per cent. of their cases. In five cases Rebaudi demonstrated the spirochetes.

In several of my cases there was a lesion at the aortic valve.

In four instances I was able to prove the presence of latent syphilis in one or both parents by the luetin or Wassermann test. In several others the absence of any venereal infection and the sudden death of a parent in early life suggested the inherited nature of their infection.

A frail lad of 24 was brought to me because it was feared that tuberculosis might be the cause of his weakness, dyspnea and chest pains. The lungs were normal but the usual signs of aortic insufficiency were present. The venereal history in both patient and his father was negative but he gave a positive luetin test as did his mother and one of two younger sisters. The father gave a negative luetin but a weak positive resulted when the test was repeated. In all, the Wassermann was negative. The only suspicious thing in the history was the fact that his mother had had several miscarriages.

Biermann[6] has reported an interesting case of arteritis of the peripheral vessels associated with dilatation of the aortic arch in a young woman of 19 with congenital lues. The lesion of the aorta was diagnosed roentgenographically. In two of my cases of congenital aortitis the Roentgen ray showed no dilatation of the arch. In a third, presumably congenital, a well marked dilatation was revealed.

Clinicians the world over have observed families in which many of the members succumbed to heart or arterial disease. This is commonly attributed to the fact that they have inherited poor material for their arterial wall and that as a result of the vicissitudes of life the artery gives way. So far as I know, it has not been suggested that syphilis might be an important

5. Roch and Weisner, quoted by Longcope, W. T.: Arch. Int. Med., January, 1913, p. 15.
6. Biermann, J.: Deutsch. med. Wchnschr., 1911, xxxvii, 1157.

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factor in these cases, yet several of the families studied suggest this possibility.

Attention has been drawn to the part played by syphilis in cardiac lesions, by Warthin[7] who concludes from his pathologic study "that syphilis, both congenital and acquired, is the most important etiologic factor in the production of cardiac disease, both myocardial and endocardial." From the clinical point of view; Schottmüller[8] reports a positive Wassermann reaction in over 40 per cent. of his cardiac cases taken as a whole, irrespective of the lesion.

A robust man of 35, who considered himself to be in perfect health, came to me as he had been refused life insurance because of heart-disease. He had a well-marked aortic regurgitation which had given no symptoms. He had had neither rheumatism nor venereal disease so far as he knew. Both the Wassermann and luetin tests were positive. His father had died of tetanus and his mother was living and in good health. Inquiry, however, developed that his father had had a slight "stroke" in his fiftieth year. His mother gave a very strong luetin reaction.

The following family is of especial interest as one member had slight angina pectoris which, I believe, has not been ascribed to congenital syphilis.

A young woman, aged 27, whose husband had been in excellent health at the time of his death from an accident a few weeks after his marriage, consulted me in 1910, with a statement that she had been doctoring for the last six years for "rheumatism." This proved to be pain of a sudden character between the shoulder blades. Tuberculosis had been feared. The physical examination was practically negative, except for a very few râles over the right chest anteriorly at the border of the sternum, and a slight tenderness over the first sternochordal junction on the left side as well as over the midthoracic vertebrae. No definite diagnosis was made at that time. The patient seemed neurotic and not very ill. Eighteen months later she said "the rheumatism had been in the left shoulder and went through the heart." She complained of soreness through the upper left side of the chest and of a very slight cough. There were still a few râles in the secondary right space anteriorly near the sternum. (I was puzzled because the pain was on the left

7. Warthin: Am. Jour. Med. Sc., 1914, cxlvii, 667.
8. Schottmüller: Therap. d. Gegenw., 1913, xv, 337.

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and the only abnormal sounds were on the opposite side.) About a year later she experienced some dyspnea in going upstairs and a soft systolic murmur was present in the second left interspace, but it was not accompanied by anemia. The upper outer border of the left trapezius muscle was found to be somewhat tender. Even at this time I did not appreciate what the condition was, as the murmur was present only in the second left space and I did not then know that an aortic systolic murmur may be heard only in the second or third left interspaces. On reviewing her family history I found, however, that her mother had had several miscarriages and that her father had had an enlarged heart and had died from angina pectoris at 58. The mother was apparently in good health, except for "rheumatism" through both shoulders and the upper part of the sternum. On examination it was found that she had a systolic murmur at the base of her heart. A sister had died from cardiac decom-

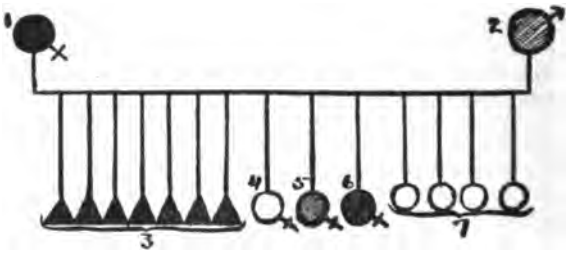

Chart 3.—Pedigree of family showing cardiac lesions. 1. Living, aged 65; aortitis; luetin +. 2. Husband died, aged 58; angina pectoris. 3. Severe miscarriages (sequence of pregnancies not known). 4. Died, aged 3 months. 5. Died, aged 30 +; decompensation following aortic regurgitation. 6. Living, aged 30; angina pectoris; aortitis (?); luetin +. 7. Not examined; one has precordial pain.

pensation secondary to an aortic regurgitation. Both my patient and her mother gave a positive luetin test. The mother's "rheumatism" subsided after a course of inunctions, and the daughter's disappeared after neosalvarsan and mercury. Two other "heart families" were met with.

A man of 53, a policeman by occupation, complained of dyspnea on exertion. He knew of no venereal infection. His heart was enlarged and a systolic murmur was present which was loudest at the base. The systolic blood-pressure was 210; diastolic 110. His father had suddenly dropped dead in his forty-sixth year, and a brother had died from a "shock" when 48. Two Wassermanns were negative but the luetin test was strongly positive.

The perfect compatibility over a period of many years, of an occult lues and good health is here shown. This man had enjoyed excellent health for over fifty

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years, yet the disease which was to rob him of his rightful expectancy of life was slowly advancing but without sign or symptom. Had a Wassermann or luetin test been possible in his early life and thorough treatment instituted, he would be living to-day in all probability. The next family further demonstrates the importance of testing the children in all cases of sudden parental death in early life.

A boy aged 14, who is not anemic, has a well-marked systolic murmur over the base of his heart, loudest on the right and extending up to the clavicle. His father suddenly dropped dead when 35 years old. His mother, aged 38, has hypertension. The boy, his mother and one sister with internal strabismus, have very strong Wassermanns, and in a younger brother the test was doubtful. An older sister gave a negative Wassermann but a positive luetin.

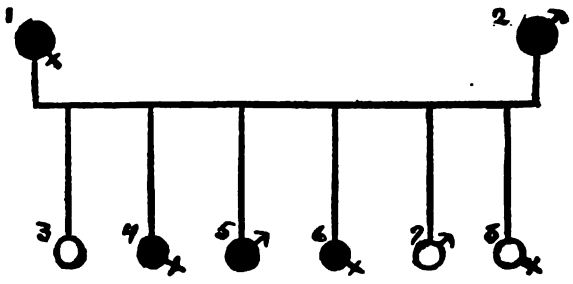

Chart 4.—Pedigree of family also showing cardiac lesions. 1. Mother living, aged 38; hypertension; Wassermann +; luetin ±. 2. Father died, "stroke," aged 35. 3. Died in infancy. 4. Living, aged 17; apparently well; Wassermann —; luetin +. 6. Living, aged 14; frail; aortitis; Wassermann +; luetin +. 6. Living, aged 8; internal strabismus; Wassermann +; luetin +. 7. Living, aged 6; frail; Wassermann ±; luetin —. 8. Living, aged 2½; apparently well; Wassermann not done; luetin —.

It has long been recognized that syphilis may cause arterial hypertension, and because of the steady increase in the mortality from arterial and kidney diseases it is important to ascertain how important lues, and especially congenital lues, is in this condition.

Hintzelmann,[9] whose original article I have not obtained, believes that congenital syphilis often causes chronic nephritis. Cassel[10] found renal changes in ten

9. Hintzelman: Ztschr. f. Kinderh., 1913, ix, No. 1.
10. Cassel, quoted by Murphy and Powers (Footnote 11).

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out of twelve syphilitic infants at necropsy and Murphy and Powers[11] state that the affection is, as a rule, a slow chronic nephritis, sometimes latent, sometimes showing acute periods.

Another interesting family is the following:

The patient, an unmarried woman of good repute, aged 45, has suffered from extreme nervousness for a number of years and now has a systolic blood-pressure of 160. Her father died at about 58 of nephritis and the mother of the same malady at 73. One brother living has hypertension and an hypertrophied heart. Two sisters are married—both are extremely nervous. One had a child, an epileptic, who died at 22. The other sister has hypertension. A fourth sister

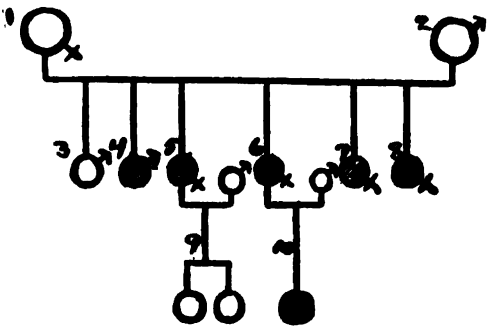

Chart 5.—Pedigree of family showing various disorders ascribable to syphilitic infections. 1. Died, aged 73; nephritis. 2. Died aged 50 +; nephritis. 3. Died in infancy. 4. Living, aged 50 +; hypertension. 5. Living, aged 50 +; hypertension; deafness in late teens. 6. Living, aged 48; neurasthenia; deafness in late teens; Wassermann —; luetin +; only daughter an epileptic (10), dying at 22. 7. Died, "withered kidney"; aged 28. 8. Living, aged 45; hypertension; neurasthenia; deafness in late teens; Wassermann ±; luetin +. 9. Apparently healthy twins.

died at 28 of a "withered kidney." All three living daughters became gradually deaf during their late teens. My patient had a doubtful Wassermann test and a very positive luetin. The sister, who was the mother of the epileptic child, gave a negative Wassermann but a positive luetin.

The next is the most remarkable family, as heart and arterial disease is present in three generations.

A little over a year ago I was called to attend an unmarried woman, aged 43, who was suffering from a greatly embarrassed heart-action and a systolic blood-pressure of

11. Murphy and Powers: System of Syphilis, Oxford Univ. Press, 1908, i, 358.

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about 270. She had lost a brother aged 16 from heart-disease, which was not secondary to rheumatism. Another brother, aged 37, is stated to have had some sort of ulcer at or near the rectum for several years, and periodically he "sheds" part of the skin from the soles of his feet. Two of his wife's three pregnancies have resulted in miscarriage. A sister, aged 45, also unmarried, has hypertension, and as a girl had an ulceration of the rectum which only healed after a very long course of treatment and was followed by a slight stricture. A married sister has suffered from headaches for years, in addition to a number of symptoms common to neurasthenia. A younger brother, aged 36, is apparently in good health. The three sisters and the apparently healthy brother all gave negative Wassermanns, but the sister with the highest blood-pressure, the neurasthenic, and the brother who seemed well, all gave positive luetin tests. The

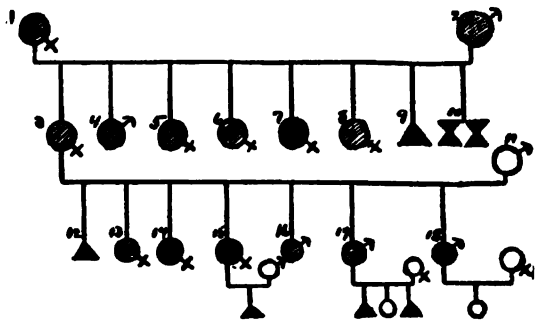

Chart 6.—Pedigree of family with cardiovascular disease in three generations. 1. Maternal grandmother died, aged 64; "apoplexy." 2. Her husband died of a "fatty heart," aged 64. 3. Died of acute dilatation of heart following pneumonia, aged 50. 4. Died, aged 17 "apoplexy." 5. Died, aged 38; "heart disease"; no rheumatism. 6. Living, aged 63; hypertension; several strokes of apoplexy; Wassermann —. 7. Living aged 60 +; apparently well; Wassermann —; luetin +. 8. Living, aged 58; was a 7-month baby; not examined; has much dyspnea. 9. Miscarriage. 10. Twins; stillborn seventh month. 11. Husband of No. 3; died of "tumor of throat." 12. Miscarriage. 13. Living, aged 45; hypertension; when a child had an ulcer of rectum very slow to heal; Wassermann —; luetin —. 14. Living, aged 43; hypertension (S. B. P. 270); Wassermann —; luetin +. 15. Living, aged 39; neurasthenia; Wassermann —; luetin +. 16. Died, aged 16; heart disease; no rheumatism. 17. Living, aged 37; not examined; has a chronic "sore" near anus. 18. Living, aged 36; apparently well; Wassermann —; luetin +. It is noteworthy that 60 per cent. of the pregnancies of the third generation resulted in miscarriages.

other brother has not been tested. The family history apparently gives the clue to the situation.

The father had died from a "tumor of the throat," the mother, from acute cardiac dilatation complicating pneumonia, at 52. Her first pregnancy resulted in a miscarriage. One of her brothers died of "apoplexy" at 17, and a sister who had not had rheumatism, of heart-disease at 38. Three

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of the mother's sisters—all unmarried—are still living. One appears to be in good health but gives a positive luetin test though her Wassermann is negative. Another, now past 60, has hypertension and several years ago had a slight stroke of apoplexy. A third, not as yet examined, was a 7-months baby and is stated to suffer severely from dyspnea on exertion. The maternal grandmother died of apoplexy at 64 and her husband at the same age of a "fatty heart."

It is especially fortunate that there were so many unmarried women in two generations, as this practically eliminates acquired infection.

This family suggests syphilis in three generations. There is no proof that the mother of the present generation, who died of cardiac dilatation after pneumonia, had lues, other than the presence of syphilis in her children. Of course it cannot be said that she might not have been infected by her husband, who may possibly have had syphilis. But the astonishingly large number of cardiovascular cases in her own generation and the positive luetin test in an unmarried sister makes the assumption that she had a congenital (myocardial) syphilis almost a certainty.

In this connection the statement might be made that an underlying and unsuspected syphilitic myocarditis is probably a more frequent cause of cardiac death in the course of other infections than we have hitherto supposed.

It would seem from this investigation that the luetin test is of more value in detecting congenital infection of long standing than the Wassermann test. This is especially true when the disease is dormant. Emory[12] has also noted this fact. Whenever possible both tests should be employed as neither is infallible. Nor does a positive Wassermann or luetin reaction guarantee that the presenting symptom is due to syphilis. In four cases the luetin test was negative, while the Wassermann was positive. In one, both tests were negative. Had cholesterinized antigens been generally employed, it is quite possible that the per-

12. Emory: Lancet, London, 1914, i, 223.

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centage of positive results would have been somewhat higher; but the luetin test was positive several times even when fortified antigens were used. The ideal method of procedure is first to obtain blood for a Wassermann and then either give mercury by mouth for a week, when the luetin test should be made, or the interval may be shortened by an injection of mercury at the time the luetin test is given.

The torpid reaction, coming on in from ten days to three weeks is common. Since using mercury in conjunction with the luetin test the indefinite reactions are rare, nearly all going on to pustule formation.

Time will not permit the discussion of the luetin test *per se* as an indication for therapeusis when occurring without obvious lesion. Nor can treatment be considered other than to say that relief of symptoms has been complete in a number of cases in which the Wassermann was persistently negative with the luetin positive. In a few there was a slight recurrence several months later, which usually promptly responded to further treatment. Whether a cure in its strictest sense is possible, only time will tell.

CONCLUSIONS

1. We must accustom ourselves to think of syphilis as a family disease. But rarely is our patient the only one infected.

2. Over half of the children born of syphilitic parents, who survive infancy, give a positive luetin reaction. In nearly 90 per cent. of those with obvious ailment the Wassermann or luetin test is positive.

3. There is often nothing in the appearance to suggest lues and the symptoms are indefinite and often misleading.

4. Too much emphasis cannot be placed on the importance of a complete family history in every obscure case.

5. It seems probable that syphilis may be transmitted to the third generation.

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6. Some cases of neurasthenia are due to congenital lues and can be promptly cured by specific treatment.

7. Syphilis appears to be an etiologic factor in certain of the families prone to heart and arterial disease.

8. Hypertension in middle life may be due to congenital lues.

9. Both the Wassermann and luetin tests should be employed as neither is infallible, the Wassermann being frequently negative in syphilis hereditaria tarda, the luetin occasionally so.

10. The examination of all venereal sores for spirochetes and their prompt treatment, controlled by the Wassermann and luetin tests, would ultimately make congenital syphilis a medical curiosity.

It is with pleasure that I acknowledge a number of valuable suggestions in the preparation of this paper from both Dr. Noguchi and Dr. Ellis of the Rockefeller Institute.

75 Pratt Street.

ABSTRACT OF DISCUSSION

Dr. Robert N. Willson, Philadelphia: Because of Dr. Cabot's challenge to the effect that "if I would show him a mitral stenosis with an etiology other than that of rheumatism he would believe in it." I present to the Section two hearts, both showing, as late manifestations of hereditary lues, a high-grade stenosis of the mitral valve in addition to other extensive involvement. In the one case the latter consisted of a ruptured aneurysm of the thoracic aorta in a child of 4 years, and, in a second, of considerable patchy atheromatous involvement of the first portion of the aorta, though the aortic valve leaflets were normal. In neither case was there at any time an indication of "rheumatic" involvement in any of its forms. In both cases (the child and adult), one parent and probably both were syphilitic. I think the final test as to the direct etiology of such cases could and should be successfully demonstrated in the post-mortem discovery of the spirochetes, as well as by the Wassermann test during life. There would, however, seem to be little need for such an ultimate study in the specimens presented at this time. Dr. Stoll's paper brings to our attention once more the growing need of assigning to syphilis a place equally as prominent as that of rheumatism in the causation of valvular lesions, and a far more significant influence in the etiology of arterial lesions and consequent secondary changes in the

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muscle of the heart. I have seen many little children with no other sign of syphilitic parentage than fibrous, whipcord vessels, those of little old men and women. In fact I have come to regard arteriosclerosis in the child as highly indicative of hereditary lues, even in the absence of all other symptoms. If such a heredoluetic survives and marries, his or her children are not unlikely to present congenital cardiac lesions which should be, though they often are not, attributed primarily to syphilis. Dr. Stoll has cited in his series an instance of mitral stenosis in a young adult female, presumptively luetic in origin. This case resembles closely in its clinical details the case in an adult represented by one of the specimens shown. One point seems to me well worth remembering in connection with these cases, namely, that many instances of arterial and cardiac disease are characterized as congenital or of unknown etiology, when a more thorough and painstaking study of the anamnesis would correctly label the lesions as heredosyphilitic or even acquired syphilis.

Dr. A. C. Griffith, Kansas City, Mo.: I have been using the luetin test for some time. When in New York a short time ago I asked Dr. Noguchi why it was that at times the luetin test was negative when we had a positive Wassermann? He answered that it was because the system was so saturated with the toxin or the poison from the spirochetes in the body that the luetin was rendered inert. If the patient was placed under treatment with mercury or salvarsan the tests all became positive.

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A STUDY OF THE ARNETH FORMULA

GRAHAM E. HENSON, M.D.
JACKSONVILLE, FLA.

Since Arneth[1] in 1904 suggested his classification of polymorphonuclear neutrophils as a guide in the prognosis of infectious diseases, while there have been a number of contributions by other authors, their work in applying the classification has been largely confined to tuberculosis, although Kagan[2] has reported his findings in cases of sepsis. In the Arneth classification the polynuclears are divided into five classes depending on the number of nuclei contained within the cell. Taking the blood from a large number of healthy persons he determined that in the normal person a

TABLE 1.—THE ARNETH CLASSIFICATION

Column	1	2	3	4	5
Percentage	5	35	41	17	2

fairly constant relative percentage of the cells was found in each of the five columns (Table 1). An increase in Columns 1 and 2 with a corresponding decrease in Columns 3, 4 and 5, he termed a shift to the left, the normal Arneth index, comprising the totals of Columns 1 and 2, being 40.

Bushnell and Treuholtz[3] adopted the method of adding one half of the number contained in Column 3 to those in Columns 1 and 2. In the series which I now

1. Arneth, Joseph: Die neutrophilen weissen Blutkörperchen, Jena, 1904.
2. Kagan, S. H.: Nuclear Classification of the Neutrophil Leukocytes and Its Relation to Disease, Boston Med. and Surg. Jour., 1910, clxii 709.
3. Bushnell, G. E., and Treuholtz, C. A.: Arneth's Method in the Clinical Study of Pulmonary Tuberculosis, Med. Rec., New York, 1908, lxxiii, 471.

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report I have preferred to take as an index the number in excess of the normal count in Columns 1 and 2; thus, a total of 50 in these columns is reported as plus 10. In classifying the neutrophils I have adhered to the rules set by the majority of previous investigators, nuclei being joined by a thread being counted as two, while those connected by a distinct isthmus were counted as a single nucleus. The greatest care has been maintained to avoid the counting of superimposed nuclei, which would result in causing a false shift to the left; when it was extremely difficult to determine with any certainty the column in which to place a cell, it was discarded. In making the differential counts, two hundred cells have been counted, and a similar

1	2	3	4	5

Polys.	Large Lymp.	Small Lymp.	Large Mono.	Eosin.	Baso.	Trans.

Blank form used in recording differential count and Arneth index.

number of polynuclears used in arriving at the Arneth formula. Wright's stain has been used in all instances with satisfactory results. To facilitate the technic in securing the differential count and Arneth index at the same time, a pad ruled as in the accompanying blank form was used.

As the white cells are counted a check is placed under the proper heading, the polynuclears put in their respective columns, according to the number of nuclei, with a total of 200 cells counted, the differential count determined and a sufficient additional number of polynuclears counted to bring their number to 200, thus arriving at the Arneth index.

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In Series A (recorded in Table 2), consisting of thirty-one unselected cases taken from the surgical service of Dr. Raymond C. Turck at St. Luke's Hospital, a total and differential white cell-count is not recorded. Cases 2, 5, 6, 9, 12, 13, 14, 18, 19, 20, 21 and 27 all showed decided shifts to the left. All of these were septic cases excepting Cases 6, 14, 21 and 27, Case 6 being a case of trifacial neuralgia in an unhealthy person, Case 14 one of exopthalmic goiter, Case 21 a compound fracture of the tibia accompanied by severe shock, and Case 27 a clean hernia, the latter showing a very decided eosinophilia; but the patient escaped from observation before further investigation of a possible causative factor could be conducted. In Case 18, epithelioma of the lower jaw with a plus index of 7.50, the patient succumbed a few weeks after admittance. The other nineteen cases in this series showed practically normal indexes, all of them clean surgical cases excepting Case 4 with a superficial sepsis recovering in two weeks, Case 8, a case of multiple fistulas recovering in three weeks, and Case 22, a case of cancer of the penis showing no recurrence eight months later. In contradistinction to the pictures in these cases attention is called to Cases 2, 5, 9, 12, 13 and 20, all of which had decided plus indexes and a slow convalescence.

Series B also consists of forty-two cases from the surgical service of Dr. R. C. Turck. The clean surgical cases only serving as a control were not used after a sufficient number had been obtained for this purpose. This series is, then, largely from selected cases. Table 3, the record of cases in Series B, in addition to giving the Arneth index, records the total white cell and the differential counts. Cases 2, 7, 8, 11, 13, 17, 19, 20, 22, 23, 25, 28, 29, 30, 31, 32, 35, 36 and 37 all show decided shifts to the left. All of them were septic cases excepting Cases 20 and 22, Case 20 being an inguinal hernia in an infant 2 years old, and Case 22 a carcinoma of the stomach, the patient deserting

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TABLE 3.—RECORD O

Case No.*	Age	Diagnosis	Treatment	I
1	10	Compound fracture of left femur; closed fracture right femur; laceration on back with infected urinary fistula.	Abduction frame; late operation on left femur.	Complete
2	10	Osteomyelitis of both tibiae; extensive superficial ulceration; positive Wassermann.	Curettage and antisyphilitic treatment.	Very muc healed; ment.
3	30	Fracture of fibula	Lane plate	Cured ..
4	9	Double talipes; equinovarus	Tenotomy; osteotomies	Cured ..
5	35	Acute appendicitis	Radical operation	Cured ..
6	40	Rectal fistula; ischiorectal abscess	Radical operation	Cured in
7	38	General peritonitis	Laparotomy; drainage	Died 12
8	36	Septic cholecystitis	Laparotomy; drainage	Cured in
9	39	Endocervicitis; lacerated perineum	Trachelorrhaphy and perineorrhaphy	Cured ..
10	42	Luetic necrosed tibia	Curettage; specific treatment	Cured ..
11	35	Infected ununited compound fracture of tibia.	Resection of necrotic bone	Still und
12	33	Chronic appendicitis and prolapse of uterus.	Appendectomy and fixation of uterus.	Cured ..
13	35	Double salpingitis	Radical operation	Cured ..
14	14	Acute appendicitis	Appendectomy	Cured ..
15	37	Endocervicitis	Trachelorrhaphy	Cured ..
16	26	Acute appendicitis	Appendectomy	Cured ..
17	12	Extensive burns followed by infection	Open air; sunlight; skin graft	Cured ..
18	30	Extensive burns followed by infection	Placental graft	Improvin
19	60	Urinary fistula secondary to suprapubic prostatectomy.	Resection	Cured ..
20	2	Inguinal hernia	Radical operation	Cured ..
21	6	Hernia; hydrocele	Radical operation	Cured ..
22	30	Carcinoma of stomach		Deserted
23	45	Empyema	Resection of rib and drainage	Unimpro
24	55	Myelitis	Laminectomy	Died ...
25	28	Extensive abscess, neck and jaws, secondary to decayed tooth.	Drainage, 3 weeks	Cured ..
26	31	Palmar abscess	Drainage, a few days	Cured ..
27	16	Osteomyelitis of tibia	Curettage	Improvec
28	30	Appendicular abscess; general peritonitis.	Drainage, etc	Cured ir
29	20	Actinomycosis lower and upper maxillary; positive uncinariasis.	Curet and drainage; thymol	Still unc
30	28	Empyema	Resection of rib; drainage	Still unc
31	13	Ruptured appendicular abscess; general peritonitis.	Drainage, etc	Died ...
32	25	Cellulitis of arm, shoulder and hand resulting from infected finger.	Drainage	Cured ..
33	17	Spastic paralysis with deformity	Tenotomies and resection of knee-joint.	Improvec
34	33	Multiple varicose ulcers of leg	Resection of saphenous; curettage of ulcers, etc.	Cured ..
35	36	Empyema of gall-bladder; perforation; general peritonitis.	Laparotomy; drainage	Died ...
36	68	Septic cystitis	Suprapubic prostatectomy	Cured ..
37	31	Acute appendicitis	Radical operation	Cured ..
38	24	Acute appendicitis	Radical operation	Cured ..
39	28	Acute appendicitis	Radical operation	Cured ..
40	10	Pott's disease	Spinal jacket	Under ts
41	42	Chronic cholecystitis of 10 years' standing.	Cholecystectomy	Died fr tis 48 tion.
42	28	Chronic appendicitis	Appendectomy	Cured ..

* In Cases 3 and 22 the patients were colored; all the others were white persons.

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F CASES IN SERIES B

Disposition	Differential Count								Arneth Count					
	Total White-Cell Count	Polys.	L. Lymph.	S. Lymph.	L. Mono.	Eosin.	Baso.	Trans.	1	2	3	4	5	Shift
cure in 7 months.	12,000	78.0	2.0	6.5	3.5	8.0	2.0	.0	7.0	30.5	47.0	12.0	3.5	...
h improved; nearly still under treat-	12,500	63.0	7.5	20.0	2.0	5.0	1.5	1.0	9.5	37.0	40.0	10.0	3.5	6.5
.....	8,000	68.0	3.0	19.5	2.5	6.0	1.0	..	8.0	30.5	47.0	11.0	3.5	...
.....	9,000	47.5	3.0	40.5	2.5	5.5	.0	1.0	4.5	28.0	55.5	9.0	3.0	...
.....	19,000	69.5	18.0	8.5	3.0	1.0	.0	0.0	7.0	29.5	45.5	10.5	7.5	...
4 weeks.....	8,000	56.0	8.5	30.0	1.5	2.0	.0	2.0	7.0	33.5	46.0	8.5	5.0	...
hours later.....	18,000	24.5	14.5	28.0	3.0	.0	.0	30.0	30.5	47.5	19.0	2.5	.5	38.0
7 weeks.....	22,500	79.0	5.0	13.0	2.0	.0	.0	1.0	22.0	46.0	29.0	2.5	.5	28.0
.....	7,000	67.5	5.0	26.5	1.0	.0	.0	.0	5.0	34.5	39.5	14.5	6.5	...
.....	7,500	72.0	3.0	19.5	2.5	2.0	1.0	.0	7.5	36.0	38.5	12.5	5.5	3.5
er treatment.....	8,500	77.0	6.0	15.5	1.0	.5	.0	.0	10.5	38.0	39.0	8.5	4.0	8.5
.....	9,000	53.5	6.0	26.0	3.5	7.5	2.5	1.0	9.5	29.5	44.0	12.5	4.5	...
.....	10,000	66.0	6.0	21.5	2.5	2.0	.0	2.0	18.0	36.5	37.5	5.5	2.5	14.5
.....	6,000	55.0	6.5	22.5	4.5	9.5	.0	2.0	12.5	26.0	44.5	11.5	5.5	...
.....	9,500	68.5	5.0	21.0	2.5	1.0	.0	2.0	9.0	33.5	49.0	5.5	3.0	2.5
.....	10,500	49.5	8.5	39.0	.5	1.0	1.0	.5	3.5	28.5	49.0	16.0	3.0	...
.....	10,000	58.5	5.0	34.5	1.0	1.0	.0	.0	17.0	38.5	40.5	3.0	1.0	15.5
g	8,000	61.0	8.0	24.0	2.0	3.0	.0	2.0	6.0	35.5	48.5	8.0	2.0	1.5
.....	8,500	64.5	7.5	25.5	.5	1.0	1.0	.0	10.5	41.5	43.5	4.0	.5	12.0
.....	15,000	26.5	4.5	64.5	3.0	1.0	.0	.5	20.5	36.5	39.5	1.5	2.0	17.0
.....	10,000	52.5	7.0	30.5	3.0	6.5	.0	.5	5.0	33.0	45.5	12.5	4.0	...
.....	8,000	49.0	11.0	35.0	2.0	1.5	.0	1.5	10.5	39.5	45.0	3.5	1.5	10.0
ved	10,000	72.0	10.5	14.5	.5	.0	.0	2.5	19.5	43.0	31.0	5.5	1.0	22.5
.....	15,000	79.5	7.5	8.5	.5	.0	.0	4.0	7.0	36.0	44.5	8.5	4.0	3.0
.....	18,000	85.5	6.5	2.0	3.5	.5	.0	2.0	18.5	43.5	29.5	6.5	2.0	22.0
....	8,000	66.5	5.5	22.0	2.0	2.5	.5	1.0	10.0	30.5	46.5	10.0	3.0	.5
l	12,000	57.0	10.5	23.5	2.0	6.0	1.0	.0	9.5	33.5	39.5	14.5	3.0	3.0
4 weeks.....	18,000	78.5	4.0	12.5	4.0	.5	.0	.5	14.5	37.5	39.0	5.0	4.0	12.0
ler treatment.....	9,000	34.0	8.0	17.5	2.0	11.5	2.0	5.0	21.0	46.5	26.5	4.0	2.0	27.5
ler treatment.....	25,000	83.0	1.5	13.5	1.0	.0	1.0	.0	15.5	54.5	24.5	4.5	1.0	30.0
.....	15,000	83.0	6.0	6.5	2.5	2.0	.0	.0	20.5	49.5	25.0	4.0	1.0	30.0
.....	10,500	77.0	2.0	19.5	1.0	.0	.5	.0	20.5	48.5	27.5	3.0	.5	29.0
l	11,00	57.0	3.0	27.5	.5	7.0	2.5	2.5	3.0	37.0	46.5	10.5	3.0	...
.....	9,000	48.0	5.5	40.0	2.5	3.0	1.0	.0	5.5	40.5	46.0	5.5	2.5	6.0
.....	9,250	69.0	9.5	12.5	1.0	1.5	.0	6.5	16.5	42.0	32.5	6.5	2.5	18.5
.....	12,600	83.0	4.5	5.5	.0	3.0	1.0	3.0	15.5	40.5	39.5	2.5	2.0	16.0
.....	7,000	70.0	4.0	20.0	3.5	.5	2.0	.0	13.5	32.5	45.5	4.0	4.5	6.0
.....	9,000	78.0	7.5	10.5	2.0	2.0	.0	.0	4.0	35.0	51.5	7.5	2.0	...
.. ..	7,800	72.0	8.5	15.5	2.0	1.5	.5	.0	5.5	30.5	56.0	6.0	2.0	...
eatment; improving.	9,000	76.5	4.0	15.5	1.0	2.0	1.0	.0	8.0	32.0	51.5	4.5	4.0	...
m acute pancreati- hours after opera-	6,000	63.5	3.0	25.5	2.0	4.0	.0	2.0	6.0	33.0	51.5	6.5	3.0	...
.....	7,200	69.5	4.0	22.5	1.5	2.5	.0	.0	5.5	34.0	52.5	4.5	3.5	...

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and being lost to observation. In the series, Cases 7, 24, 31 and 35 with plus indexes of 38, 3, 30 and 18.5, and Case 42 with a normal index, succumbed shortly after operation. Cases 1, 6, 18, 27 and 40, in which there was no shift, were of a nature that would lead us to expect one. It is significant, however, that three of these are in children, which, together with the blood-picture in Case 20, an infant, indicates that the Arneth formula, like the general blood-picture, is subject to a wide variation in infants and young adults.

In a further series of twenty-five cases of pulmonary tuberculosis I have been able to confirm the findings of Arnold C. and Henry Klebs,[4] Minor and Ringer[5] and Cummings,[6] in which they found a decided shift to the left in unfavorable cases.

In a smaller series of typhoid fever cases I also found a shift to the left in severe infections, while in malaria fever and pellagra there seems to be no change from the normal Arneth picture. I hope to have the opportunity to report in detail on this work at some future time. My findings up to the present would lead me to think that in certain classes of cases the Arneth index is of some prognostic value, enough so at least to warrant a careful and intensive study of the blood-picture in all septic and infectious diseases.

I wish to acknowledge my deep appreciation to Dr. Raymond C. Turck, chief surgeon of St. Luke's Hospital, for the privilege of studying the blood of his patients, and for many other courtesies extended to me while the work was in progress.

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SALVARSAN IN THE TREATMENT OF PERNICIOUS ANEMIA

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Few diseases have baffled the internist and therapeutist as has pernicious anemia. Much has been written concerning its symptomatology, etiology and pathology, but little has been added to the treatment of this disease.

To Addison belongs the credit of first calling attention to this condition. How comprehensive do we find his original characterization of the disease: "A general anemia occurring without any discoverable cause whatever, cases in which there had been no previous loss of blood, no exhausting diarrhea, no chlorosis, no purpura, no renal, splenic, miasmic, glandular, strumous or malignant disease." To this description Biermer has added the pathologic findings and Ehrlich the characteristic blood-picture.

In contrast to all this how small do we find the space devoted to the treatment of this condition. At the start we are confronted with the authoritative statements of Osler, that "in the true Addisonian cases, the outlook is bad," or the results of Cabot's exhaustive study of 1,200 cases, that there "were only six cases in which recovery is known to have occurred."

All are familiar with the usual methods of treatment, including the necessity for prolonged rest, adherence to good hygiene, plenty of fresh air and an abundance of nourishing food. From time to time new drugs are offered as being beneficial in the treatment of pernicious anemia, but all observers, sooner or later, return to arsenic administered in the form of

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Fowler's solution, arsenious acid, atoxyl or sodium cacodylate. Bone-marrow extracts have been used.

Following Hunter's important studies, there was considerable employment of such drugs as salol and beta-naphthol with the hope of inhibiting bacterial growth in the gastro-intestinal tract. In extreme cases the transfusion of human blood has been advocated and occasional brilliant results noted. Reports of the removal of the spleen in the treatment of this condition have recently appeared, but the results are far from convincing.

In June, 1912, Bramwell reported a series of seven cases of pernicious anemia treated with salvarsan. To this number in May, 1913, he added four more cases. Of these eleven cases he reports four as having been "apparently completely cured; striking improvement in two cases, considerable improvement in another with ultimately a relapse and death; in one case slight improvement and death from bronchopneumonia while under treatment; in two cases there was no improvement; in one case slight improvement, the patient still being under treatment."

Hobhouse reports a most encouraging result obtained in a patient treated with two injections of 0.3 gm. of salvarsan resulting in an increase in the red blood-cells from 800,000 to 4,704,000, and hemoglobin from 18 to 110 per cent(?). Hobhouse believes that the high hemoglobin in this case was due to the iron which the patient took later on in his treatment. Boggs, in his review of the literature up to May, 1913, adds eleven more cases all treated with salvarsan. He cites seven cases treated at the Johns Hopkins Hospital with the following results: One case received but a single injection of 0.3 gm. of salvarsan; death followed forty-eight hours later from myocardial degeneration and there was no improvement in the blood-count. Another patient received a single injection of 0.2 gm. and died eleven days later, no change being noted in the blood-count. The five remaining cases all "showed improve-

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ment, with an initial drop in the blood-count never more than 200,000." These cases, however, also received in addition to the salvarsan, Fowler's solution or sodium cacodylate, so that the improvement cannot be attributed to the salvarsan alone. In Boggs' own experience at the Baltimore City Hospital, four patients were treated, "all of whom showed favorable reaction to the salvarsan in the regeneration of the blood, and the relief of the symptoms." In one case there was a "most remarkable cure of a patient in his fifth relapse" who was quite refractory to both Fowler's solution and sodium cacodylate, but under intravenous injection of salvarsan in 0.3 gm. doses every four weeks, there was marked improvement in the blood from 500,000 to 5,000,000 and hemoglobin from 23 to 90 per cent. in sixteen weeks. Personal communication (March 10, 1914) to me states that this patient still continues to do well.

Friedlander and Maynard each report a single case treated with salvarsan, and in each instance there was marked improvement following the injection of the drug.

Since the appearance of the reports of Bramwell and Boggs, I have had seven cases under observation. All seven cases have received salvarsan intravenously with the following results: Summary: 7 cases, 5 males, 2 females all over 40 years of age; symptoms present for more than one year in all cases. Average hemoglobin on admission 29 per cent.; lowest 20 per cent., highest 60 per cent. Average red blood-count on admission 1,100,000; lowest 850,000, highest 2,700,000. Intravenous injections of salvarsan in doses of 0.4 to 0.6 gm. were given at intervals of two to three weeks, the largest number of injections given to any one case being six over a period of four months. With the exception of one case in which dilute hydrochloric acid was given for a few days after admission, no other drug was given. Four of these cases are at the present time doing well, with blood in satisfactory condition.

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One patient recently died, probably of myocardial trouble, which condition was present during the period of observation. The blood even up to the time of his death continued to show improvement after each injection. On admission his hemoglobin was 21 per cent., red blood cell-count 960,000; after three injections of 0.6 gm. of salvarsan, during a period of thirteen weeks, the hemoglobin increased to 68 per cent. and red blood-count to 3,224,000. Another patient, whose blood-count on admission was 850,000 and hemoglobin 20 per cent., received two doses of salvarsan, and although his blood showed but slight improvement, there was much relief of his subjective symptoms, and he refused further treatment. In this patient a positive Wassermann reaction in the blood-serum was obtained, and the marked improvement in his symptoms may be due to this fact. Another patient, a farmer, aged 56, has received two injections, and his blood has begun to show evidence of response to the drug. He is still under observation. To illustrate the favorable reaction to the salvarsan in the regeneration of the blood the following case is cited:

A physician, aged 57, was admitted, Dec. 15, 1913, complaining of "exhaustion and weakness on exertion." Symptoms had been present over a period of fourteen months, during which time he took "bottles of tonics" and "blood medicines," including Fowler's solution. At the time of admission he presented the appearance of a typical case of pernicious anemia. The blood-picture showed red blood-cells 1,272,000; white blood-cells 3,500, hemoglobin 32 per cent. Following the first intravenous injection of salvarsan there was a slight decrease in the number of red blood-cells, but within a week's time this initial drop was regained, and after each succeeding injection, as shown in the accompanying chart, there was continued improvement in the red blood cell-count.

No untoward symptoms have followed the injections, though occasionally the patient complains of a slight headache and a little nausea. There has been no marked febrile reaction in any of the cases.

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The method of giving the salvarsan is simple and does not require elaborate apparatus. A graduated cylinder of 250 c.c. capacity; a 20 c.c. Luer all glass syringe, a three-way cock, rubber tubing and a medium-sized Record steel needle comprise the outfit.

PREPARATION

The salvarsan is dissolved in 200 c.c. of 0.5 per cent. saline made up *freshly* distilled water, sterilized by boiling; the acidity of the salvarsan is neutralized with

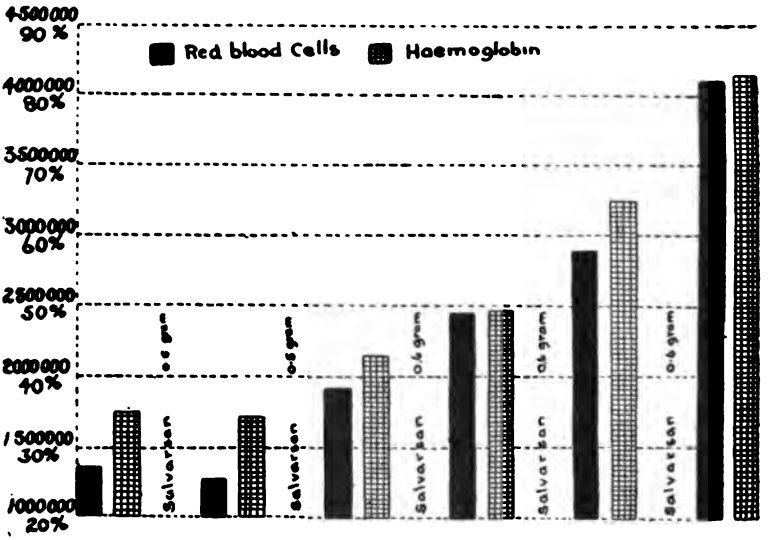

Chart illustrating Case 5: Increase in red blood cell-count and hemoglobin following intravenous injections of salvarsan.
Dec. 26, 1913: R. B. C., 1,272,000; hemoglobin, 35 per cent.; salvarsan, 0.5 gm.
Jan. 3, 1914: R. B. C., 1,184,000; hemoglobin, 35 per cent.; salvarsan, 0.5 gm.
Jan. 12, 1914: R. B. C., 1,896,000; hemoglobin, 42 per cent.; salvarsan, 0.6 gm.
Jan. 22, 1914: R. B. C., 2,448,000; hemoglobin, 48 per cent.; salvarsan, 0.6 gm.
Feb. 6, 1914: R. B. C., 2,708,000; hemoglobin, 65 per cent.; salvarsan, 0.6 gm.
April 14, 1914: R. B. C., 4,010,000; hemoglobin, 82 per cent.

15 per cent. sodium hydroxid. The solution and neutralization are performed in the graduated cylinder which is later made to serve as a reservoir. By placing in the neck of the graduated cylinder a rubber

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stopper equipped with two small glass tubes and connecting one of these by means of the rubber tubing to the three-way cock, the syringe and needle attached, and by inverting the cylinder, one may have a reservoir which will keep the system full of fluid and do away with the trouble of air-bubbles. The injection is made in the usual way. The solution is introduced slowly, ten to fifteen minutes being required for injecting 200 c.c.

REPORT OF CASES

CASE 1.—T. S., male, aged 50, farmer, admitted Aug. 7, 1913. Complaint, "weakness and numbness in the fingers, difficulty in walking." Symptoms date over a period of eighteen months, red blood-count 960,000, hemoglobin 21 per cent. After three injections of 0.6 gm. salvarsan during a period of thirteen weeks, the hemoglobin increased to 68 per cent. and red blood-count to 3,224,000. Patient was up and around and worked a little on his farm, but on April 4, 1914, "caught a cold" and after a few days' illness died suddenly, probably of myocardial trouble, which condition was present during the period of observation.

CASE 2.—L. W., female, aged 41, admitted Nov. 13, 1913. This patient was referred to the sanatorium by Dr. Olin, Watertown, N. Y., through whose kindness I have permission to report her previous blood examination. April 3, 1913, red blood-count 1,190,000, hemoglobin 60 per cent. April 12, salvarsan 0.5 gm. given intravenously. May 6, red blood-count 1,730,000, hemoglobin 70 per cent; June 16, hemoglobin 80 per cent., red blood-count 2,500,000, salvarsan 0.6 gm. given intravenously; August 20, red blood-count 3,370,000, hemoglobin 87 per cent. Patient had a slight return of her symptoms during the months of October and November and there was slight decrease in red blood-count; under rest and diet, the condition of the blood improved, and Dec. 19, 1913, red blood-count was 4,656,000, hemoglobin 78 per cent.

CASE 3.—L. V., a pharmacist, aged 50, admitted September, 1913. Complaint, "weakness and anemia." Symptoms present over one year. Sept. 20, 1913, 20 per cent. hemoglobin, red blood-count 850,000. Was given 0.6 gm. of salvarsan intravenously. In two weeks' time the red blood-count showed but slight increase to 968,000 and the hemoglobin to 25 per cent. October 23, salvarsan 0.6 gm. intravenously resulted in very little change in the blood-count. Despite the slight improvement in the blood condition, there was noticeable improvement in his general condition, the patient feeling much stronger, and some gain in weight. A positive Wassermann reaction may account for the beneficial action of the salvarsan in this case.

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CASE 4.—C. M., female, aged 40. Complaint, "anemia." Admitted July 25, 1913. On admission, red blood-count 1,612,000, hemoglobin 25 per cent. Patient was given two doses of 0.4 gm. of neosalvarsan at intervals of ten days. August 20, red blood-count was 2,856,000 and hemoglobin 38 per cent. Patient left the sanatorium and home physician writes that she "continued to improve and that her blood is almost normal."

CASE 5.—I. N., physician, aged 57, admitted Dec. 15, 1913. Complaint, "exhaustion and weakness on exertion." Symptoms present over a period of fourteen months. Red blood-count 1,272,000; white blood-count 3,500, hemoglobin 32 per cent. Thus far he has received six intravenous injections of 0.6 gm. salvarsan with resulting marked improvement in his general condition and in the red blood-count (for blood-counts see chart). This case is interesting in that he was most refractory to Fowler's solution and his condition showed no improvement under its use, previous to the injection of salvarsan.

CASE 6.—F. C., male, aged 54, farmer, admitted April 16, 1914, complaining of "stomach trouble," symptoms present two years. On admission red blood-count 1,840,000, hemoglobin 36 per cent. Patient was given 0.6 gm. of salvarsan intravennously. Count of blood made four days later showed little change. A second injection of 0.6 gm. salvarsan resulted in an increase in red blood-count and improvement in patient's condition. He insisted on leaving the institution, and letters from patient tells of his steady improvement, so much so that he is up and about and attending to his little farm.

CASE 7.—L. M., male, aged 56, schoolteacher, complaint "shortness of breath," symptoms present ten months. Red blood-count on admission, 992,000, hemoglobin 28 per cent. Following the injection of salvarsan, 0.6 gm., there was slight increase of red blood-cells to 1,352,000 and hemoglobin 33 per cent. This case is disappointing in that the patient would not remain under observation but left soon after the first injection.

CONCLUSIONS

It is obvious from my cases and from those cited in the literature that it is too early to draw any conclusions as to the possibility of obtaining permanent improvement or cure of pernicious anemia by salvarsan. In a disease characterized by its chronicity and its tendency to relapse, it seems rather improbable that such a result will be achieved, at least with our present methods.

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Salvarsan in a single dose is of doubtful value. In fact, in our cases it has been the rule usually that no improvement in the blood was noted till after the second injection of the drug; but from this point onward our impression is that the improvement has been steadier and more rapid than with any other method of treatment. This view, however, may require revision, owing to the small number of observations.

In cases refractory to arsenic in other forms, salvarsan should be given a thorough trial.

A very low red count is probably not in itself a contra-indication to the use of salvarsan.

The results thus far obtained in the treatment of pernicious anemia by salvarsan are sufficiently encouraging to warrant an extended trial of the drug.

I am indebted to Miss G. W. Parker for her assistance in making the blood-cell counts.

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8. Maynard: Brit. Med. Jour., 1913, i, No. 2715.

ABSTRACT OF DISCUSSION

DR. W. E. ROBERTSON, Philadelphia: The type of anemia originally described by Addison represents, in all probability, a group of disease entities all of which show a similar blood-picture. Some of these we are now able to recognize as cases of uncinariasis, bothriocephalus latus, gastric carcinoma, ankylostomiasis, perhaps even chronic paludism and splenic anemia and possibly, too, severe metallic poisoning of a chronic type—lead, for instance. While I should not care to regard the remaining cases, clinically looked on as pernicious anemia, as being due always to lues, a certain proportion of them doubtless are. I recently had a case in my ward at the Episcopal Hospital in Philadelphia, clinically a case of profound pernicious anemia, having both a typical blood-picture and an achylia gastrica. There was a history of lues of fifteen years' standing, with a positive Wassermann in the serum. The patient would not permit

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a study of the spinal fluid. After a single intravenous injection of 0.6 gm. of salvarsan he made a complete recovery, the blood-picture returning absolutely to normal, the patient gaining 30 pounds in weight within the next four months. Careful laboratory studies on the serum and spinal fluid will probably solve an appreciable fraction of our diagnostic problems.

Dr. W. W. Tompkins, Charleston, W. Wa.: Will Dr. Brotherhood state how long salvarsan was used in pernicious anemia before good effects were noted? What quantity was employed? Incidentally, did Dr. Brotherhood give Fowler's solution at the same time? With regard to calling this disease pernicious anemia, I think a better name would be syphilitic anemia. I am inclined rather to look on pernicious anemia as a disease without known cause.

Dr. Robert N. Willson, Philadelphia: It would be interesting, in the light of Dr. Brotherhood's success in the treatment of pernicious anemia by salvarsan, to consider again the etiology of the disease. Especially would this seem advisable when we remember that not a few cases of typical pernicious anemia have been reported which have developed a complete clinical picture of tabes, and several of tabes with paresis. I had the privilege of studying a family a number of years ago of which three sisters developed pernicious anemia, and two of them the clinical picture of tabes. A brother died at 68 of "mental trouble." Two other brothers are invalids, one having had an anterior poliomyelitis and later on glaucoma in one eye. Still another brother has kidney trouble with "puffing under the eyes." The likelihood that this is a family of heredosyphilitics is strong, and the occurrence in its midst of several instances of pernicious anemia is all the more interesting. I published the photographs of sections of the cord in one of the sisters, showing lesions of the posterior columns more than usually like those of tabes. The typical cord involvement seen in pernicious anemia is a degenerative vacuolization of the nerve-cells, succeeded by a replacement gliosis. Hemorrhages are frequent, and cavity formation occasional. Very typical is the lacework appearance of the tissue due to the dropping out of the nerve-fibers. There is seldom present an implication of the gray matter with contraction or shrinking of the cord such as one sees in true tabes. The posterior columns may alone be involved, but the lateral columns are never the only seat of pathologic change. Usually the condition is a combined sclerosis, the lateral columns and occasionally later the anterior horns taking part in the process. The use of neosalvarsan and of salvarsan in concentrated solution, by means of direct intravenous injection through a Record syringe, is coming more and more into vogue, as

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its safety seems more certainly established. Should this method of using the drug continue to appear justified, salvarsan therapeusis will be brought promptly within the scope and range of the general practitioner.

Dr. E. Lindeman, New York City: My experience with blood transfusion in pernicious anemia comprises a series of from thirty-five to thirty-eight cases. A number of these cases had been treated with neosalvarsan intravenously, but the results were not at all encouraging and blood transfusion had to be employed. I was particularly interested in the Wassermann reaction and was impressed with the fact that approximately 15 per cent. yielded a positive reaction. I would congratulate Dr. Brotherhood on his results.

Dr. Thomas Grier Simonton, Pittsburgh: I should like to report one case of pernicious anemia in which I used salvarsan. This patient was a woman, 40 years of age, with red cells 800,000 and hemoglobin 30 per cent. Salvarsan was used. On the first day the percentage of hemoglobin remained the same. Before she died the amount of hemoglobin was slightly increased, but there was a marked destruction of the red blood-cells. She went into coma on the sixth day after injection and died.

Dr. Tom A. Williams, Washington, D. C.: The pathologic appearances in pernicious anemia as described, do not differ from the pathologic appearances found in any kind of anemia, whether or not its etiology is known. The appearances differ entirely in either tabes or other types of syphilis. The cord changes in pernicious anemia are due to the permeability or friability of the blood-vessels, in consequence of which an exudate of plasma escapes into the cord and destroys portions of it, generally in an irregular fashion; so that there is not a system disease, properly speaking, because of them. If there is, however, a focus low down in the posterior column, there will be an ascending degeneration just as one finds in tabes dorsalis consequent on the involvement of the posterior roots in a syphilitic leptomeningitis. Again, if the exudates occur in the lateral columns, we may find spastic symptoms because of the implication of the crossed pyramidal tracts. As a rule, however, the sclerosis which ensues on the exudation is scattered in such a way as to create the clinical picture known as mixed sclerosis, which easily distinguishes it clinically from tabes dorsalis. In syphilitic endarteritis, however, we may find the clinical cord-picture not unlike that seen in pernicious anemia, although, pathologically, the picture is entirely different, the alteration of the nervous tissues occurring in endarteritis not from exudate, but from ischemia. As a rule the clinical differentiation is not difficult.

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Dr. J. S. Brotherhood, Clifton Springs, N. Y.: I did not intend to advocate salvarsan as a panacea in the treatment of pernicious anemia. In the treatment of our cases no other drug than salvarsan was used. The results thus far obtained are sufficiently encouraging to warrant an extended trial of this agent. The transfusion method was not applicable in some of my cases; in all the salvarsan was given intravenously. The drug was given in rather large doses, as much as 0.6 gm. per dose, and repeated at intervals of two weeks. With regard to the transfusion of blood in these cases, Dr. Lindeman, no doubt, finds that in his cases the patients are in bad shape when they arrive in the hospital and the transfusion is a *dernier ressort*. In my cases it required from ten to sixteen weeks before the blood exhibited a normal picture. I have succeeded in getting a count of 4,800,000 red cells and a hemoglobin close to 90 per cent., in one case. Before I began to use salvarsan it was my custom to give Fowler's solution in 5 minim doses, three times a day, increasing the dose 1 drop a day until the patient is taking from 30 to 40 drops a day.

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STUDIES IN LIVER FUNCTION *

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In recognition of the need of better criteria for judging of the functional capacity of the liver in disease, this investigation was undertaken to determine (1) the degree and frequency with which functional changes can be demonstrated in anatomically diseased livers, (2) in what clinical types of liver injury the functional changes are most marked and (3) the diagnostic and prognostic value of these changes. In other words, an attempt has been made to regard the liver, in disease, from a physiologic point of view, and to study its various functions with the hope of ascertaining its behavior under pathologic conditions.

THE FUNCTION OF THE LIVER IN HEALTH

In health the liver has three well-established functions: 1. The glycogenic function, which has to do with carbohydrate metabolism, and consists in (*a*) the conversion of the monosaccharids (dextrose, levulose and galactose) into glycogen; (*b*) the temporary storage of that glycogen as such, and (*c*) the reconversion of it by enzyme activity into dextrose as needed in the body. 2. A participation in nitrogenous metabolism which consists in the conversion of certain nitrogenous bodies (ammonia, amino-acids, etc.), into urea. 3. The production of bile.

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In addition, the liver apparently plays a part in the production of fibrinogen and antithrombin, although the connection of the latter functions with the liver is not so well established as the first three mentioned.

THE TESTS OF LIVER FUNCTION

The following tests based on well-known physiologic functions of the liver have been employed:

1. *Carbohydrate Metabolism.* — In this connection two tests have been employed, namely, Strauss'[1] levulose test and Bauer's[2] galactose test. The former consists in the ingestion of 100 gm. of levulose on an empty stomach and the examination of the urine voided during the next few hours to determine the presence or absence of the sugar, using Fehling's and Seliwanoff's tests. Bauer's is similar to Strauss' test except that 30 gm. of galactose are used instead of 100 gm. of levulose. The ingestion of these sugars in the amounts indicated does not result in their appearance in the urine in normal individuals, according to Strauss. Their appearance in the urine is due to a decrease in tolerance for these substances, indicative of decreased functional capacity of the liver.

2. *Nitrogenous Metabolism.*—In relation to nitrogenous metabolism and liver function a study of the nitrogen partition in the blood and in the urine has been made. If the liver converts the ammonia and amino-acids of the blood into urea, then it might be expected that in liver injury we should find a decrease in the urea percentage of the total non-protein nitrogen of the blood and an increase in the amino-acid nitrogen of the blood, while in the urine we might expect to find a decrease in the relative amount of urea with an increase in the ammonia and amino-acids. (The view that the liver is not wholly responsible for the conversion of the ammonia and amino-acids of the blood

1. Strauss: Berl. klin. Wchnschr., 1898, xxxv, 398; ibid., 1899, xxxvi, 159; Deutsch. med. Wchnschr., 1901, xxvii, 757.
2. Bauer: Wien. med. Wchnschr., 1906, lvi, 20.

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into urea has recently received support from the work of Folin[3] and Van Slyke[4] and of Fiske and Sumner.[5])

3. *Urobilinogen.*—It has been maintained by many observers that the presence of urobilinogen in the urine is indicative of liver disease. Urobilinogen determinations were made in the majority of cases, but owing to the appearance of the recent comprehensive work of Wilbur and Addis,[6] and to our own unsatisfactory results, these determinations were discontinued. These investigators showed conclusively that observations on a single or a twenty-four-hour specimen have no significance, since tremendous variations occur from day to day, and that only where repeated observations are made over a period of at least two weeks and then only when control studies of the urobilin content of the feces have been made to exclude blood destruction as a factor in the production of urobilinogen can findings be accepted.

4. *Fibrinogen.*—There is evidence to show that the liver is active in the formation of fibrinogen, and Whipple[7] has suggested that the determination of the amount present in oxalated plasma may be used as an index of liver function.

5. *Lipase.*—Whipple[8] has also suggested that the estimation of the lipolytic activity of the blood may constitute a test of liver function.

6. *Phenoltetrachlorphthalein.*—This drug was introduced by Rowntree, Hurwitz and Bloomfield[9] as a test for hepatic function, and clinical studies by them

3. Folin: Jour. Biol. Chem., 1912, xi, 87.

4. Van Slyke, D. D.: Jour. Biol. Chem., 1913, xvi, 213; Protein Assimilation, abstr., THE JOURNAL A. M. A., April 12, 1913, p. 1183.

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9. Rowntree, Hurwitz and Bloomfield: Bull. Johns Hopkins Hosp., 1913, xxiv, 327.

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and experimental studies by Whipple and co-workers[8] showed that a normal excretion could be established and that many liver injuries, particularly of severe grades, were associated with a decided decrease in the phenoltetrachlorphthalein output. Further studies with this test have been carried on.

7. *Fibrinolytic Ferment.*—Dr. Goodpasture of the pathologic staff was already interested in the presence of a fibrinikytic ferment in the blood in liver cirrhosis when this work was undertaken. Samples of blood from all our patients were submitted to him for study, and through his courtesy we present the results of his studies, details of which will appear later. The ferment is specific for fibrin, does not attack fibrinogen and is destroyed by heating to 56 C. (132.8 F.).

METHODS AND NORMAL LIMITS OF TESTS

Phenoltetrachlorphthalein.—This test was employed according to the method described by Rowntree, Hurwitz and Bloomfield, details of which are given in full in their publication.[9] The lower limit of normal excretion is considered to be 30 per cent. in forty-eight hours after the intravenous injection of 400 mg. of the substance. In health, phenoltetrachlorphthalein is practically never excreted in the urine after injection of such amounts.

Fibrinogen. — The heat coagulation method as described by Whipple[10] was used in these determinations, and values below 350 gm. per hundred c.c. were regarded as abnormal.

Lipase.—Determinations of the lipolytic activity of the blood were made, using Loevenhart's[11] method, which consists in the determination of the total acid production of the blood when exposed to known quantities of ethyl butyrate at 37 C. (98.6 F.). The result is expressed as the number of cubic centimeters of tenth-normal acid produced by 1 c.c. of plasma and

10. Whipple: Am. Jour. Physiol., 1914, xxxiii, 50.
11. Loevenhart: Am. Jour. Physiol., 1902, vi, 331.

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0.26 c.c. ethyl butyrate, diluted to 4 c.c. and allowed to react for from twenty to twenty-four hours. The upper limit of normal has been taken to be 0.40 c.c. of tenth-normal acid.

The Nitrogen Partition in the Blood and Urine.—The total non-protein nitrogen of the blood was estimated by the micro-Kjeldahl method of Folin and Denis,[12] with slight modifications, as suggested by Dr. B. B. Turner.[13] The urea percentage of the total non-protein nitrogen of the blood was determined by Marshall's[14] method, utilizing soy bean urease, and values below 40 per cent. have been regarded as abnormal. The amino-acid determinations were made by Van Slyke's[15] method. As yet, data concerning the amount of amino-acids present in the blood of normal individuals are scarce, but from a study of patients who were practically normal, 3 mg. per hundred c.c. of serum has been the value regarded as the upper limit of normal for the free amino-acid nitrogen.

The total nitrogen of the urine was determined on twenty-four-hour specimens collected under toluol by the Kjeldahl-Gunning method, the urea by Marshall's[16] and the ammonia by Folin's[17] method. The distribution of the urinary nitrogen between urea and ammonia has been shown to be dependent on the total excretion of nitrogen. The normal limits of the various nitrogenous constituents of the urine, with varying levels of nitrogen excretion, are therefore hard to define sharply. However, one can probably safely conclude that with a urinary nitrogen excretion of 10 gm. or more, the lower limit for urea nitrogen is 80 per cent. and the upper limit for ammonia nitrogen is 5 per cent., while with a nitrogen excretion of from 5 to 10 gm., the lower limit for urea is 70 per cent. and the upper limit for ammonia is 8 per cent.

12. Folin and Denis: Jour. Biol. Chem., 1912, xi, 527.
13. These modifications will be described shortly by Dr. Turner.
14. Marshall: Jour. Biol. Chem., 1913, xv, 487.
15. Van Slyke: Jour. Biol. Chem., 1912, xii, 399.
16. Marshall: Jour. Biol. Chem., 1913, xiv, 283; xv, 495.
17. Folin: Ztschr. f. physiol. Chem., 1902, xxxvii, 161.

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Furthermore, excessive acid production in the organism is accompanied with a lowering of the urea percentage and an increase in the ammonia percentage. The free amino-acid in the urine was determined by Van Slyke's[18] method, and 1.5 per cent. has been adopted as the upper limit of normal. Future work may change these values.

SUMMARY OF FINDINGS

Forty-five cases have been studied in this series, in nearly all of which some abnormality of the liver was thought to be present. Some of the cases called cirrhosis were certainly not far advanced, and in some instances it appeared that the diagnosis was not definite, differences in opinion being frequently encountered. On account of lack of space the details of the cases are not given here,[19] but a summary of the results obtained is given in Table 1.

Column 1 shows total number of tests made, Column 2 the total number of positive results, while the remaining columns show the number of positive results in the various diseases. The figures in italics indicate the number of cases in which each particular test was applied in the particular disease studied, while the other figures indicate the number of positive findings in the particular disease.

From this table it will be seen that the following results were obtained: The *phenoltetrachlorphthalein test* was applied in the feces in 42 cases with 16, and in the urine in 34 cases with 21 positive. *Fibrinogen* was determined in 40 instances, 8 of which were below 350 mg. and 12 below 400 mg., while 8 were above 800 mg., that is, 20 abnormal findings. The *lipolytic activity* of the blood was investigated in 39 cases, 5 of which showed an acid production of more than 0.4 c.c. and 3 above 0.5 c.c. The presence of *fibrinolytic fer-*

18. Van Slyke: Jour. Biol. Chem., 1913, xvi, 121.
19. Findings of all tests, clinical notes, necropsy findings in fatal cases together with a discussion of the functional findings appear in the article in the Proceedings of the Society of American Physicians, 1914.

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TABLE 1.—SUMMARY OF FINDINGS

	Total Number of Tests	Total Number of Positive Tests	Cirrhosis of Liver		Myocardial Insufficiency		Carcinoma		Syphilitic Hepatitis		Pernicious Anemia		Poly-serositis		Miscel-laneous	
Number of Cases tested	..	..	..	14	..	12	..	3	..	2	..	2	..	2	9	10
Phthalein in feces	42	16	14	6	9	1	3	2	2	1	2	2	2	0	9	4
Phthalein in urine	34	21	11	7	10	5	3	2	2	1	1	0	2	2	5	4
Fibrinogen	36	8	14	6	11	1	1	0	2	0	—	—	2	0	1	1
Fibrinolytic ferment	40	7	14	7	12	0	1	0	2	0	—	—	2	0	9	0
Lipase	39	5	14	2	11	1	1	0	2	0	—	—	2	0	9	2
Galactose	29	4	11	2	7	0	1	0	2	1	1	0	2	0	4	2
Levulose	18	2	10	2	8	0	0	0	—	—	1	0	1	0	3	0
Blood:																
Urea-N %	37	9	14	5	12	1	1	0	2	1	—	—	2	2	6	0
NH_3-N	35	25	14	10	9	7	1	1	2	1	—	—	2	1	6	4
Urine:																
Urea-N %	41	11	14	3	11	3	2	0	2	2	2	1	2	0	8	2
NH_3-N %	41	28	14	10	11	7	2	0	2	2	2	2	2	2	8	5
NH_3-N %	22	12	7	5	6	2	1	0	1	2	1	0	1	1	5	2

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ment was tested for in 40 instances, and found in 7, all of which were cirrhoses. The *galactose* test was applied in 29 and the *levulose* in 19 cases, the former showing only 4 and the latter 2 positive findings. The *total non-protein nitrogen* and *urea nitrogen of the blood* were determined in 37 cases. The urea nitrogen was less than 40 per cent. of the total in 9 instances. The *amino nitrogen of the blood* was determined in 35 cases, and amounted to more than 3 mg. per hundred c.c. in 25 instances and above 4 mg. in 13 instances. The *total nitrogen urea and ammonia in the urine* were determined in 41 cases. The total nitrogen of the urine was above 10 gm. in 13 cases, and in these the urea nitrogen was below 80 per cent. in 7 instances, and the ammonia nitrogen above 5 per cent. in 10 instances. Twenty-one cases showed a urinary nitrogen between 5 and 10 gm., and of these, 4 cases showed a urea nitrogen below 70 per cent. and 11 an ammonia nitrogen above 8 per cent. The *amino-acid nitrogen* content of the urine was investigated in 22 cases, 12 of which showed values above 1.5 per cent. of the total nitrogen.

Liver Cirrhosis.—The results in the fourteen cases of cirrhosis studied were as follows: Phenoltetrachlorphthalein studied in feces in 14, positive in 6, in urine in 11, positive in 7; fibrinogen in 14, positive in 6; lipase in 14, positive in 2; fibrinolytic ferment in 14, positive in 7; galactose in 11, positive in 2; levulose in 10, positive in 2; urea nitrogen percentage (blood) in 14, positive in 5; amino nitrogen (blood) in 14, positive in 10; urea percentage (urine) in 14, positive in 3; ammonia percentage (urine) in 14, positive in 10; amino nitrogen percentage (urine) in 7, positive in 5.

Myocardial Insufficiency.—Twelve cases of myocardial insufficiency were studied. Phenoltetrachlorphthalein studied in feces in 9 cases with 1 positive, lowest being 18 per cent., and in urine 10 cases with 5 positives; fibrinogen in 11 with 1 positive; lipase in

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11 cases with 1 positive; fibrinolytic ferment in 12, positive in none; galactose in 7, positive in none; levulose in 3, positive in none; urea nitrogen percentage (blood) in 12, positive in 1, in which 6 were over 50 per cent., and 3 over 60 per cent.; amino nitrogen (blood) in 9, positive in 7.

The functional injury in liver cirrhosis is relatively greater than in chronic passive congestion, for a consideration of all the tests in each condition indicates that in 10 of the 14 cases of cirrhosis there was definite functional injury, 3 with less marked injury and only one with a practically normal function throughout, while in chronic passive congestion only 4 showed definite decrease, while 7 showed a practically normal function.

Carcinoma of Liver.—Little data outside of the phenoltetrachlorphthalein have been collected. C 28, who definitely had metastasis to the liver,[20] showed a 23 per cent. output five months before death. H 29, with gastric carcinoma and clinically thought to have metastasis to the liver, showed a 24 per cent. output, phenoltetrachlorphthalein positive in urine and the urea only 21 per cent. of the total non-protein nitrogen of blood. These cases are in keeping with the three cases of liver carcinoma reported last year in which the phenoltetrachlorphthalein excretion was 8, 14 and 7 per cent., respectively. However, a slight decrease in phenoltetrachlorphthalein, for instance, from 20 to 25 per cent. does not indicate liver carcinoma, since such findings have been found in gastric carcinoma when no proof of liver metastasis was at hand, in which case it is merely the expression of the influence of anemia and cachexia on liver function.

Anemia. — Clinically, a severe grade of anemia depresses the function of the liver as indicated by phenoltetrachlorphthalein. That there is also a decrease in the fibrinogen has been shown by Whipple, but

20. Details of these cases can be found in the article in the Proceedings of American Physicians.

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owing to the quantity of blood necessary for carrying out the test, it is not applicable in all cases of anemia. Changes in the urinary nitrogen partition may appear.

Luetic Hepatitis.—Of the two cases studied, one showed normal phenoltetrachlorphthalein, a low lipase, urinary nitrogen partition changes and a positive galactose, while the other showed a low phenoltetrachlorphthalein content in feces, positive in urine, an abnormally high fibrinogen, low urea percentage of total non-protein nitrogen in blood and urinary nitrogen partition changes.

Polyserositis.—Two cases with much the same clinical condition and both with large livers showed practically identical findings, for instance, normal phenoltetrachlorphthalein in feces, but positive in urine, fibrinogen and lipase normal, low urea percentage of total non-protein nitrogen in blood, and changes in urinary nitrogen partition, but no decreased tolerance for sugar.

THE PHENOLTETRACHLORPHTHALEIN TEST

Previously the results of eighty applications of the test on sixty-seven patients were reported. The total number of patients studied to date is 113, thirty-three of whom had no clinical evidence of liver disease. The positive findings in health and in various types of liver disease, together with the appearance of the drug in the urine, are shown in Table 2.

TABLE 2.—POSITIVE FINDINGS IN HEALTH AND IN LIVER DISEASE

	Examined	Less Than 30 Per Cent.	Urine Examined	Positive
Normals	33	2	22	3
Cirrhosis	18	9	11	7
Congestion ..	32	11	10	6
Carcinoma of liver	6	6	3	2
Carcinoma ..	5	3	3	2
Luetic liver..	5	2	2	1
Severe anemia	9	7	1	0
Miscellaneous.	5	2	2	2
Totals	113	42	54	23

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NECROPSY CASES

In this series five cases came to necropsy, and pathologic findings controverting the functional findings have not been encountered. It is of interest to note that two of the cases which clinically were thought to be cirrhosis of the liver, but showed slight functional changes, proved, at necropsy, to have no cirrhosis at all, but to be cases of chronic peritonitis in which the liver was enlarged owing to a thickened capsule. In one instance, a case of cirrhosis, microscopic study of the liver suggested greater injury than was shown by the functional studies. In the six cases which came to necropsy last year there was harmony between the anatomic and functional findings of the phenoltetrachlorphthalein test.

RELATIVE VALUES OF TESTS

The series of cases is not sufficiently large to draw far-reaching conclusions as to the relative values of the different tests, but the following impressions have been received:

(*a*) Phenoltetrachlorphthalein: A phenoltetrachlorphthalein output in the feces below 30 per cent. or its appearance in the urine is infrequent in health and frequent in anatomically diseased livers. A normal output does not exclude liver injury.

(*b*) Fibrinogen: Low values are frequent in cirrhosis, but inconstant. Very low findings may carry prognostic significance.

(*c*) Lipase: Determination of lipolytic activity of blood furnishes little or no information of diagnostic or prognostic value in these types of cases.

(*d*) Bauer's galactose and Strauss' levulose tests yielded very little information in this series.

(*e*) Dr. Goodpasture's fibrinolytic ferment studies on this series of cases show that this ferment is present only in cirrhosis and hence when present is of diagnostic value.

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(*f*) Blood Nitrogen Partition: Urea nitrogen was low in several instances and especially low in cases of advanced cirrhosis. Amino-acid nitrogen was high in a considerable proportion of the cases.

(*g*) Urinary Nitrogen Partition: The ammonia and aminonitrogen were increased in most of the cases studied, particularly in cirrhosis. Owing to the non-exclusion of acidosis considerable difficulty is experienced in interpreting these results. It would have been advisable to have attempted to exclude acidosis by the feeding of alkalies.

PRACTICABILITY OF TESTS

The phenoltetrachlorphthalein test involves an intravenous injection and careful collection of stools for forty-eight hours. Three undesirable features are connected with its application: 1. The quality of red color obtained in certain instances (from 10 to 20 per cent. of the cases) is such that accurate quantitative estimation is difficult. Only in rare instances is this a serious difficulty leading to error of more than 5 per cent. 2. Thrombosis frequently follows at the point of injection, as evidenced by slight local pain or tenderness together with resistance offered to the palpating finger along the course of the vein. This occurred in eight instances in this series of cases, but in no case has it occasioned serious discomfort or resulted in actual harm to the patient. 3. With salt solution made with freshly distilled water chills following the injection are infrequent. When no dilution is employed chills are less frequent and not accompanied with increase in temperature.

Fibrinogen determinations are inapplicable in the presence of severe anemia. They necessitate the withdrawal of from 40 to 50 c.c. of blood. A high speed centrifuge and considerable chemical equipment are requisites. The test is time-consuming. *Lipase determinations* require neither complicated apparatus nor much time. *The determination of the total non-*

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protein nitrogen, urea nitrogen and amino-acid nitrogen of the blood cannot be carried out when severe anemia exists. Technically the determinations are easy but are time-consuming. *The nitrogen partition* in the urine requires somewhat less time. *Galactose* can be administered without discomfort to the patient, but technical difficulties attend the use of *levulose,* at least 25 per cent. of the patients refusing to take the full amount or developing nausea or vomiting following its ingestion. *The fibrinolytic ferment* is readily demonstrated. *Urobilinogen determinations* in the urine are valueless unless made daily for a period of two weeks and unless associated with urobilin determinations in the feces.

CONCLUSIONS

1. Outspoken changes in liver function can be demonstrated in most cases of advanced liver cirrhosis, in markedly congested livers associated with myocardial insufficiency, in carcinoma of the liver, in luetic livers and in conditions of cachexia with marked anemia.

2. Functional changes have been most marked in cirrhosis, neoplasm of the liver and in cachectic conditions associated with severe grades of anemia. Functional changes in chronic passive congestion have not been frequent or pronounced.

3. Harmony in the findings of the tests is present in some cases, that is, most of the tests indicating either a decrease function or a normal function. However, lack of harmony is striking in other cases.

4. Concerning the relative merits of these tests the impressions that have been received are that the determination of the phenoltetrachlorphthalein excretion, the fibrinogen, and the nitrogen partition in the blood and urine are of decided value in revealing the presence of, and to a less degree the extent of, functional involvement, while the demonstration of a fibrinolytic ferment is of decided diagnostic impor-

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tance. The determination of the sugar tolerance and of the lipolytic activity of the blood apparently afford information of much less value.

The information derived from these studies on the liver does not compare in diagnostic and prognostic value with that derived from corresponding studies of the kidney. This may depend on several factors, namely, (*a*) the inadequacy of our knowledge of liver physiology; (*b*) the limited number of cases and of types of severe liver injury under observation; (*c*) the possible existence of a great "factor of safety" in the liver, whereby in case of necessity function is carried on efficiently by a relatively small proportion of liver substance; (*d*) the fact that the prognosis in many of these cases is controlled by factors other than decreased liver function, and (*e*) the lack at present of correlation of anatomic, clinical and functional findings occasioned by the newness of the subject. The results, however, encourage us in the belief that scientifically and also clinically this subject is worthy of extensive investigation.

ABSTRACT OF DISCUSSION

Dr. William S. Thayer, Baltimore: In the Johns Hopkins Hospital we believe that these tests have brought us somewhat nearer to an understanding of liver disease, but there is still much to be done. The tetrachlorphenolphthalein test for hepatic function is by no means of so clear a value as the phenolsulphonephthalein test for renal function, but the work may well lead to something in the future.

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VARIOUS TYPES OF LUES

A CLINICAL AND LABORATORY STUDY. THE ABELIN REACTION. DIRECT SUBDURAL INJECTIONS

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The clinical history of syphilis, admittedly one of the most protean of all diseases, is in the process of being rewritten, and when the chapters are relatively complete it will be found that we are indebted rather to the laboratory worker than either the internist or neurologist for our more complete knowledge. It was at one time supposed that syphilis of the nervous system was a late manifestation of the disease, and this statement is generally true from the clinical point of view. Precocious syphilis was the term employed by Gowers for those cases in which patients manifest organic nervous phenomena within a year from the appearance of the primary lesion. For many years it has been recognized as a possibility, and cases have been reported by Gowers, Fournier, Oppenheim, Nonné and others, including a striking instance recently furnished by Gregory and Karpas of a case of cerebral syphilis occurring six months after the development of the primary lesion. In going over some of the patients and records in the hospital at the naval home in Philadelphia, with Dr. Stokes, formerly surgeon-general of the U. S. Navy, I was struck with the greater virulence of the disease in general and the serious and occasionally early involvement of the nervous system occurring in sailors who had contracted the disease in the Orient. It is solely from the clinical point of view,

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however, that we of to-day are justified in regarding syphilis of the nervous system as among the later phases of the activity of the treponema. Soon after the use of salvarsan became general, considerable discussion arose as to the part it apparently played in causing involvement of various cranial nerves and other more or less pronounced nervous symptoms. Previously free, involvement became manifest within a few hours or days following an injection of the drug. Routine study of the cerebrospinal fluid from luetic patients revealed to Dreyfus, that about 80 per cent. of late primary and early secondary cases show distinctive pathologic changes in the spinal fluid (cytologic increase or increase in protein content and more rarely a positive Wassermann). Thus, the explanation of the preceding, essentially a Herxheimer reaction, local or diffuse, depends on the distribution of the treponemas, and is due to the liberation of toxins resulting from the lytic action of salvarsan on the parasite. This carries with it the thought, first, that all initial doses should be small, and secondly, if symptoms of involvement of the nervous system occur, it is not necessarily a contra-indication to the further use of the remedy, but rather the reverse, though in small doses. Even the few early cases which we have felt justified in submitting as illustrative, show well the pathologic changes in the spinal fluid and there is absolutely no doubt from the point of view of the serologist, that the vast majority of luetics, from the date of the primary infection, are essentially candidates for syphilis of the nervous system. Though they may not present a single symptom, the treponemas invade all parts of the body within a day or two at most from the time of infection. Neisser succeeded in inoculating animals with blood taken from monkeys five days after the original infection and with splenic pulp taken on the twelfth day. Hoffmann has shown that monkeys may be infected by using the blood from a human in the secondary stage, and that under such circumstances

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the incubation stage in the monkey is shortened. Infection successively passaged through a series of animals increases the virulence of the infection and shortens the incubation period. Flügel recovered the treponema from the blood of a woman with a secondary, maculopapular eruption. Indeed, it is probable that the eruption is in the nature of a parasitic embolism similar to the rose spots of typhoid fever, which are mycotic, congested, capillary loops. Veillon and Girard selected a typical maculopapule and excised it on the third day after it appeared. The capillaries were dilated and congested with an early, perivascular, lymphocytic infiltration, and treponemas were found, by the silver method, in and about the capillaries. Neisser, Buschke, Levaditi, Tomasczewski, Noguchi and others have found the parasite in tertiary lesions of the skin and various organs including the nervous tissue, either by direct staining methods or by inoculation into animals. Von Zeissl found records of more than 150 cases of facial paralysis, deafness or retinitis occurring within one year of the period of original infection. Thus it is evident that every stage of the disease is potentially infective; the possibility of transmission, however, becoming less in direct proportion to the elapsed time since the original infection. Two interesting points assert themselves in connection with the primary infection and later relapses, both revolving about the initial lesion. The knowledge that syphilis may be contracted without the development of a chancre, and the well-known evanescence of secondaries in some cases, should render us tolerant in our judgment of those from whom no history is obtainable. Jonathan Hutchinson has reported several cases, one in a nurse and several in physicians, in whom the disease followed a punctured wound, the first evidences of actual infection being adenopathy and eruption. This possibility has since been confirmed experimentally. A chancre is only possible when cutaneous or mucous membrane infection occurs. Again, we sometimes see a patient

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in whom a chancre has developed, often atypical, to be sure, who admits exposure months or even a longer period in the past, but who denies recent infection. Keogh, in 1911, called attention to the fact that, in relapses occurring even at long periods after salvarsan has been given, whether the Wassermann be positive or negative at the time of the relapse, the clinical picture is more or less a replica of the condition presented at the time the patient first sought treatment. Thus, if treatment is given in the primary stage, a relapse is often manifested as a chancre, secondary stage—secondaries. Keogh regards this as a true latency, unlike the apparent latency of cases treated with mercury, which, as a rule, assume a far more advanced type in the relapse.

Briefly, then, the present concept of syphilis is that, in its earlier stages, it is a septicemia with more or less involvement of the nervous structures and coverings from the beginning. In the course of time, for some unknown reason, special predilection is manifested for some particular organ or tissue, after a period of apparent latency which only serologic study will reveal. In some instances, indeed, the latency is so well concealed that only a provocative Wassermann, as first suggested by Gennerich and almost simultaneously by Milian, will reveal it. This test is practically a Herxheimer reaction and proves the presence of treponemas somewhere in the body, hence their lysis and the subsequent successful application of serologic diagnosis. Recognizing the comparative frequency of early involvement of the central nervous system, as shown by the serologist, it would seem advisable to make studies not alone of the serum, but also, in every case of lues or suspected lues, to make routine examination of the spinal fluid, and to control treatment by subsequent studies, and, finally, to determine a cure by provocative injections governed by complete laboratory observations. It is not too much to claim that such a

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plan would in all probability prevent the development of the more destructive forms at present so common among us.

As to types of lues, it is only possible to speak in very general terms. Except for the rare cases in which a chancre fails to develop and those in which secondaries are fleeting or suppressed, the most constant and fairly uniform stage is the septicemic or secondary period. Beyond this we may speak of pernicious anemic or other blood dyscrasias, of cardiovascular, visceral, osseous, ulcerative cutaneous, central nervous (including special sense-organs) and congenital types, but each of these groups presents many varieties. Serologically, we are also unable to speak of definite types. We believe, however, that when a standard technic is developed, especially with reference to the Wassermann reaction, and particularly when we reach a conclusion as to the proper antigen to use, less criticism will be levelled against its diagnostic value than is unfortunately the case at present. Even under existing conditions, the chief critics are those who possess no laboratory experience. Until such time it might be of value, in reporting laboratory results, to mention the antigen employed and the particular form of complement-deviation test used in the work, and especially the former. Using an alcoholic antigen prepared from fetal syphilitic liver, a sheep hemolytic system and the method as given by Citron, only varying the complementary strength to obtain relative quantitative results instead of using the continental method of a definite 0.1 c.c. of guinea-pig's serum, it will be found that the large majority of late primary cases, and all untreated secondary cases will give a positive serum, and very rarely a secondary will give a positive Wassermann in the spinal fluid. The majority of secondary cases will also show some other spinal fluid change, as increase in protein content or an increase in cell-count, with prompt reduction of Fehling's solution. Latent cases occasionally give

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negative Wassermann in serum and fluid, with a positive Wassermann in the serum as the rule, though they may give changes in the protein content of the fluid; but in these cases a reaction may be invariably provoked. The majority of non-latent tertiary cases give positive serums and more marked pleocytosis or protein increase and occasionally a positive spinal fluid Wassermann. Of the nervous forms, tabes is the most frequent. A very small number is serologically negative, but these are rare. The majority have a positive serum, a positive Wassermann in spinal fluid, a moderate pleocytosis and a more or less marked Nonné and less often a positive Noguchi. Since we have used spinal fluid in amounts of 0.5, 1.0 and 1.5 c.c., we have rarely had negative Wassermanns. In the cases clinically marked by severe pain, the cell-count is usually higher, and other evidence of inflammation of the root-zones and meninges is shown by marked Nonné or Ross-Jones and Noguchi reactions. A large proportion of this type also gives a positive Wassermann in the spinal fluid. When strong positive Wassermann is obtained in both serum and spinal fluid, in most instances there is a more or less pronounced pleocytosis up to 50 or 60 possibly per cubic millimeter, with protein increase and often a positive Lange (gold solution). These are the least amenable to treatment and are spoken of as Wassermann-fast types, though not by any means invariably so.

The unilateral type of tabes and those cases presenting but one or two symptoms, as pupillary rigidity and Westphal's symptom, present no special serologic type differing from any of the above. There is one clinical phenomenon of great value diagnostically, which occurs in the vast majority of tabetics and one which is not sought for routinely, but which furnishes strong collateral proof of the existence of tabes often at a time when very few criteria are manifest. We refer to that which Collier Martin has termed the tabetic sphincter. Digital examination of the rectum

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reveals external sphincter paresis. Firm lateral pressure is painless and results in more or less relaxation of the anus so that a good view of the lower part of the rectum is obtained. This relaxation may not be overcome for a period varying from a few seconds to some minutes.

The greater the degree of meningeal involvement the higher the cell-count and the greater the protein content. Hence, in cerebrospinal syphilis, the high count is found except in the purely endarteritic forms. In some of the cerebrospinal cases the serologic picture closely simulates that of paresis, except that it is far more amenable to treatment than is paresis. Hence a serologic diagnosis is of value not alone in a diagnostic sense, but of great importance from the prognostic point of view.

In general paresis the rule is to find a strongly positive Wassermann in both serum and spinal fluid, a moderate pleocytosis and a marked protein reaction. Until very late in the course of the disease, the serum is always positive, but in a small proportion of cases the spinal fluid Wassermann may be negative throughout. Paresis frequently falls under the Wassermann-fast group, and in most instances the Lange, gold solution, runs a parallel course with the Wassermann of the spinal fluid. These laboratory results and our failure to make satisfactory serologic or clinical impress on the types of lues involving the nervous system, when combined therapy by mouth and intravenously was employed, led us to take up subdural work. We had made attempts to recover phenolsulphonephthalein, methylene blue and formaldehyd from the spinal fluid but without success, and we had never observed an icteric spinal fluid in any case of jaundice. We were, therefore, ready to accept the view that the best if not the only way to reach the nervous tissue is by direct methods. We found, too, that when we used a direct subdural injection of neosalvarsan without a previous intravenous injection, we were able to

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recover arsenic in the urine in a few hours, showing that absorption had certainly taken place. Tilney, before the New York Neurological association, reported some experimental evidence along these lines. He used trypan-blue, a vital stain, injecting 0.1 per cent. into cats and allowing them to live for twenty-four hours. At the expiration of that time, when a subdural injection had been given, the dura mater was intensely stained, the brain stained diffusely. The viscera were not stained. Microscopically he found the trabeculae of the pia extending into the brain and cord were stained, also the walls of the blood-vessels. The ganglion-cells and nerve-fibers were not stained. It seemed, therefore, that the dye found its way into the nervous tissue along the trabeculae and by the blood-vessels. Intra-arterial injection caused skin and visceral staining but none in the brain or cord or the meninges. Intravenous injection resulted in staining of the dura, pia and pituitary, though less than by intraspinal injections. Frozen sections showed the cord unstained. Subcutaneous injection resulted similarly to the arterial, the nervous tissues were unstained, but the viscera were stained.

Sicard employed ink by the lumbar subdural route in animals. In from two to four hours he found particles in the cerebellar region and still later in the region of the peduncles and within the ventricles. In from twelve to fourteen hours he found them also in the cortex of the cerebrum. He observed also that substances in solution in the cerebral fluid were removed by osmosis while particulate substances were removed by leukocytic phagocytosis. In spinal anesthesia it is well known that, if the dose be large and the specific gravity of the injected fluid be low, within a brief period, often a matter of a few minutes, both respiratory disturbance and vomiting will occur. We know also that the subdural fluid and that of the ventricles communicates normally through the foramen of Magendie at the apex of the fourth ventricle and

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through the foramina of Luschka at the outer margins of this same ventricle. Both on anatomic grounds, therefore, and on the basis of experimental evidence we are justified in our belief that better results must ensue in early cases of syphilis of the nervous system if subdural treatment is resorted to; and as many of the cases also have more or less cutaneous, visceral or osseous lues, the combined intravenous and subdural routes seem to be indicated in those whose infection during the earlier period has not been studied and treated in sufficient detail to prevent the more serious manifestations from arising.

To arrive at the approximate dosage of neosalvarsan given subdurally when 12 c.c. of a 40 per cent. solution are employed after an intravenous of 0.9 c.c., we took the figures of Bischoff, who found the total volume of blood in the bodies of two executed criminals to be 7.1 per cent. and 7.7 per cent. respectively. Thus, to a patient weighing 150 pounds, each cubic centimeter of serum could contain about 0.00017 mg., and 12 c.c. about 0.002 mg. We then employed the Abelin reaction to determine the presence of arsenic in serum and urine. Using dilutions of known strength we obtained the following figures.

1:100	Beautiful red contact ring
1:10000	Reddish ring
1:20000	Brownish ring
1:20000	Brownish ring
1:40000	Brownish ring
1:50000	Very faint brownish ring
1:60000	Negative

We were unable to obtain a reaction in the serum of blood removed in ninety minutes, in any case, and we have found a negative in one case and weakly positive in another at the end of sixty minutes. In the urine we were unable to recover it after ten hours. After intramuscular injections we did not examine the serum, but in the urine we obtained the reaction in thirty-one and forty-eight hours respectively. Abelin found practically the same results, though in two of his series he obtained the reaction in the urine in sev-

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enteen and twenty-two hours. We found the reaction positive in the serum in from ten to fifteen minutes after the intravenous injection was given. The early disappearance of the Abelin reaction led us to take the blood in from thirty to forty-five minutes after the intravenous injection was completed. We have treated nine cases in all, two by the Swift and Ellis alone, two by the direct method alone, and five by combined Swift and Ellis and direct methods. Despite the experience of Wechselmann and Marinesco and more recently the experimental evidence of Swift and Ellis, we determined to try the effect of direct injections without previous intravenous. The maximum dose employed was 0.02 gm. of neosalvarsan, and the minimum 0.006 mg. In all dosage we found the direct method too irritating. After a total of 11 direct injections, we found that the three paretics suffered the least, two of them having to be catheterized, one during the first twenty-four hours, one only at the end of the third day, and the paretic who had received 0.02 c. gm. and 0.01 c. gm. at different times, had no symptoms at all. Of the cases of taboparesis and tabes, all the direct injections were followed by severe pain, causing retention necessitating the use of the catheter for as much as two weeks and obstinate constipation. The direct injections were given in salt solution to one patient only, while in the others we employed the patients' inactivated serum in salt solution, a 40 per cent. dilution. It is well known that irritative phenomena occur after the Swift and Ellis method, so that if, as Ravaut claims, hypertonic salt solution robs the direct injection of the irritating effects of neosalvarsan, it might be well to use hypertonic salt solution as a basis for the dilution in the method of Swift and Ellis. One very advanced case of taboparesis, No. 28 of our series, was treated by the method of Swift and Ellis and by the direct method at various times. The patient finally died. Grossly, a little congestion of the meninges was found at necropsy, but sections studied by

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W. G. Spiller failed to show definite evidence of irritation. One case of paresis treated by both the direct and indirect methods, No. 34, shows marked improvement after failure to make any impress by seven intravenous injections given at weekly intervals and a number of injections of sodium cacodylate in 15 grain doses. The other two paretics are *in statu quo*. Two of the tabetics have shown marked improvement clinically, Nos. 26 and 27. They have received but two Swift and Ellis injections each. On the other hand, we have had two cases of tabes not included in our series, one with absent knee-jerks and lightning pains, the other with pupillary rigidity, absent knee-jerks, vomiting without pain, paresthesia and tabetic sphincter, both of whom recovered under intravenous treatment and mercury and iodids by mouth. The former, less marked, made an absolute recovery clinically and serologically, the latter has become subjectively symptom-free, knee-jerks now being present by reinforcement, vomiting, paresthesia and lightning pains totally relieved, the pupillary rigidity uninfluenced, serum now negative, but spinal fluid has not as yet been examined. These cases prove our previous statement that if recognized early, and this includes careful clinical and serologic study, tabes may prove amenable to intravenous injections together with mercury and iodids by mouth. In later cases, the value of the Swift and Ellis and direct methods are still *subjudice*.

REPORT OF SPECIFIC CASES

SECONDARY, TERTIARY AND CONGENITAL WITHOUT CEREBRO-SPINAL SYMPTOMS

CASE 1.—P. F., aged 18. Chancre on lip of about four weeks' duration. Was treated at once with mercury by mouth. Has a diffuse maculopapular rash. Wassermann of serum 4 plus; luetin, negative.

Spinal fluid: Cell count and Nonné, negative; Noguchi, slightly positive; Fehling's reduced; Wassermann, 1.0 and 1.5 c.c., all dilutions negative.

Abelin Reaction: Blood-serum after 0.5 neosalvarsan intravenously, positive after fifteen and thirty minutes was weakly positive after sixty minutes and after ninety minutes negative.

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Washed blood-clot. Was laked and an attempt made, by means of the Abelin reaction, to determine the presence or absence of arsenic. Unsuccessful owing to the color similarity of laked blood and Abelin reaction.

CASE 2.—M. S., aged 30. Chancre on penis five weeks ago. Has been taking pills. Has an indurated scar on foreskin. General adenopathy. Maculopapular eruption on chest. Wassermann of serum, 4 plus.

Spinal fluid: Cell-count, 10 lymphocytes; Nonné and Noguchi, negative; slight reduction of Fehling's; Wassermann, 0.2 and 0.4 c.c., negative in all dilutions.

Phenosulphonephthalein Test: First hour, 15 per cent.; second hour, 37 per cent.

Abelin Reaction: Blood-serum after 0.5 gm. neosalvarsan intravenously, positive after fifteen and thirty minutes, was weakly positive after sixty minutes and negative after ninety minutes; intravenous neosalvarsan given Nov. 13, 1913.

Urine: Markedly positive in three and one half hours; weakly positive in five and one half hours; negative in eight hours. After 0.3 gm. neosalvarsan intramuscularly, given Nov. 23, 1913, was weakly positive in one hour, positive in three, weakly positive in five, positive in eight, twelve and twenty-four hours, weakly positive in thirty-one, negative in thirty-three hours.

CASE 3.—M. N., aged 20. History of chancre five months ago, followed by eruption and constitutional symptoms. Has been taking pills ever since. Has mucous patches. General adenopathy. Scar on foreskin. Wassermann of serum, 4 plus; luetin, negative.

Spinal fluid: Cell-count, 20 lymphocytes; Nonné and Noguchi, negative; Fehling's reduced; Wassermann, 0.5, 1.0, and 1.5 c.c., negative in all dilutions.

CASE 4.—L. M., aged 24. History of suppurating sores on penis one year ago, followed by slight rash and constitutional symptoms at which time he took pills for two months. Now has a diffuse inflammation of throat. Wassermann of serum, 4 plus; luetin, negative.

Spinal fluid: Cell-count, negative; Nonné and Noguchi, slightly positive; Fehling's reduced; Wassermann, 0.5, 1.0, and 1.5 c.c., negative in all dilutions.

CASE 5.—T. B., aged 19. Chancre of five weeks' duration. Has a maculopapular rash on chest and abdomen. General adenopathy. Wassermann of serum, 4 plus.

Spinal fluid: Cell-count, negative; Nonné and Noguchi, negative; Fehling's reduced; Wassermann, 0.2, 0.4 and 0.8 c.c., negative in all dilutions.

CASE 6.—J. S., aged 48. Denies knowledge of chancre on penis. Has been taking pills for rash on body last ten days. Has syphilitic iritis. General adenopathy. Profuse maculo-

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papular eruption, large papular and papulonodular syphiloderms. Examination revealed typical chancre on penis. Wassermann of serum, 4 plus; luetin, positive (pustule).

Spinal fluid: Cell-count, negative; Nonné and Noguchi, negative; Fehling's reduced; Wassermann, 0.5, 1.0 and 1.5 c.c., negative in all dilutions.

CASE 7.—T. B., aged 38. A patient with well-defined chronic diffuse nephritis. Denies venereal history. No previous treatment. Has a papular rash on arm and leg. Wassermann of serum, 4 plus.

Phenolsulphonephthalein Test: Percentage first hour, 0; second hour, 5, on admission. Convulsion same day. After purges and sweats, thyroid gland and Fischer's enteroclysis, first hour, 15 per cent., second hour, 10 per cent.

Spinal fluid: Cell-count, 30 lymphocytes; Nonné and Noguchi, negative; Fehling's reduced; Wassermann anticomplementary reactions. Six months later, during which time mercury by mouth was given, Wassermann of serum had gradually become negative; luetin, negative.

Spinal fluid: Cell-count, negative; Nonné and Noguchi, slightly positive; Fehling's reduced; Wassermann, 0.5 c.c. —, 1.0 c.c. —, 1.5 c.c. ±.

Phenolsulphonephthalein Test: After a few months' treatment, first hour, 25 per cent., second hour, 27 per cent.

CASE 8.—T. P., aged 30. Chancre on penis, 1903. Mercurial treatment the following eight months. Neosalvarsan at another hospital, March, 1914, and later in the Episcopal hospital. For past year has been complaining of hoarseness and cough. Has a tertiary syphilitic involvement of nose and throat. Had been taking mercurous iodid. Wassermann of serum, negative. Wassermann made six weeks after second intravenous of neosalvarsan, during which time protiodid was given. Luetin, positive (papule).

Spinal fluid: Cell-count: 20 lymphocytes; Nonné and Noguchi, slightly positive; Fehling's reduced; Wassermann, 0.5, 1.0 and 1.5 c.c., negative in all dilutions.

CASE 9.—O. P., aged 42. Gumma of liver. Family history, negative. No history of previous illness. Denies venereal infection.

Present Illness.—Was well prior to seven weeks ago, at which time he developed diarrhea, vomiting, indigestion and ascites. Lost 13 pounds in weight.

Physical Examination: Liver enlarged from fourth interspace to 5 cm. above the umbilicus, is nodular. Left lobe larger, more nodular and extended farther down than right lobe. Ascites, 4.4 liters of fluid withdrawn which later recurred and 4.2 liters were removed. Wassermann of serum, 4 plus. Phthalein test, 30 per cent the first hour, second hour, 20 per cent. Gastric analysis showed a hyperacidity. Urine contained a trace of albumin and no casts. Mercury

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administered by inunctions. Potassium iodid was given; 0.45 gm. of neosalvarsan injected intravenously and another injection of 0.6 gm. intramuscularly was given some days later. Patient markedly improved, the liver reduced in size. Fluid did not reaccumulate. Gained weight, felt subjectively better.

CASE 10.—J. H., aged 43. For some years subject to sore throat. Underweight. Always cold. Multiple lesions on penis nineteen years ago. Promptly recovered; no internal treatment. August, 1913, developed dull pain in epigastric region without reference to meal. Sense of discomfort in bending and unable to sleep on left side on account of sense of weight in epigastrium. Gastric analysis, normal.

Physical Examination.—Irregular enlargement of left lobe of liver, extending down almost to transverse umbilical line. Spleen not enlarged. Diagnosis, gumma. Moderate general adenopathy. Absent knee-jerks even on reinforcement. No urinary phenomena, no lightning pains. No paresthesias, no Romberg. No ataxia.

Dec. 2, 1913: Wassermann of serum, 4 plus.

Dec. 7, 1913: Intravenous 0.6 gm. salvarsan. Protiodid then given.

Dec. 18, 1913: 0.3 neosalvarsan intramuscularly. (Gumma much reduced in size.)

Dec. 29, 1913: Patient has gained considerable weight and has lost all muscular pains promptly, considered by him rheumatic. 0.3 gm. neosalvarsan intramuscularly. Protiodid has been continued all this time.

Jan. 17, 1913: Gumma totally disappeared. Liver normal in outline. No longer feels cold; 0.9 gm. neosalvarsan intravenously. Beginning Jan. 24, 1914, a series of hypodermatic injections of sodium cacodylate in 10-grain doses, eight in all, given. Feb. 28, 1914, Wassermann of serum, 4 plus. Inunctions then started and continued intermittently for some weeks, with salivation on several occasions. All medicine then stopped for three weeks and May 13, 1914, Wassermann of serum, 3¾ plus.

Spinal fluid: Cell-count negative; Nonné and Noguchi slightly positive; Fehling's reduced; Wassermann, 0.5, 1.0 and 1.5 c.c. all negative.

CASE 11.—F. R., tobacco salesman, aged 66. Family history, negative. Suppurative sore on penis fifteen years ago. Treated with mercury for three years.

Present Illness.—For past six months has complained of weakness, shortness of breath, dizziness. Recently lost 30 pounds in weight. No indigestion. No loss of blood.

Physical Examination.—Patient is poorly nourished. Skin is of a lemon color. Muscles soft and flabby. No bleeding areas. No apparent focus of infection. Old scar on penis,

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evidence of an old destructive lesion. Urine: Specific gravity, 1.010, a cloud of albumin, hyaline and granular casts. Gastric analysis: Free hydrochloric acid, 0; total acidity, 40; lactic acid, negative. Stools: ova and occult blood negative. Blood picture: Red blood-cells, 740,000; white blood-cells, 6,000; hemoglobin, 35 per cent. Differential count: Polymorphonuclears, 70 per cent.; mononuclears, 8 per cent.; transitional, 2 per cent.; lymphocytes, 17 per cent.; eosinophils, 3 per cent. Poikilocytosis and marked anisocytosis. No nucleated reds. Wassermann blood-serum, 4 plus. Given 0.2 gm. of neosalvarsan intravenously, iron administered. One month later, blood-picture was: Red blood-cells, 1,480,000; white blood-cells, 4,880; hemoglobin, 40 per cent. Differential count: Polymorphonuclears, 48.6 per cent.; mononuclears, 1.6 per cent.; lymphocytes, 49.3 per cent.; eosinophils, 0.66 per cent. No nucleated reds. Poikilocytosis and marked anisocytosis. Mixed treatment administered. Nine months later patient was markedly improved. Appears well. Feels subjectively well. Gained weight. Free from symptoms. Normal blood-picture after six months and no further evidence of achylia gastrica. Wassermann of serum made at that time, 3 plus. Considering himself well, he refused further treatment, but has recently developed an iritis.

Case 12.—M. McD., aged 20. A case of congenital syphilis. Has paralysis of left leg from an attack of anterior poliomyelitis when a child. Necrosis of the left toes. Wassermann of serum, 4 plus; luetin, positive (papule and vesicle).

Spinal fluid: Cell-count, Nonné and Noguchi, negative. Fehling's reduced. Wassermann, 0.5, 1.0 and 1.5 c.c., negative in all dilutions.

Case 13.—H. K., aged 30. Congenital syphilis. Interstitial keratitis. Has always been in good health. Has typical physiognomy of hereditary syphilis. Hutchinson's teeth. Severe interstitial keratitis in the left eye. Wassermann of serum, 3 plus; luetin, positive (pustule).

Spinal fluid: Cell-count, negative; Nonné and Noguchi, positive; Fehling's reduced; Wassermann, 0.2 and 0.4 c.c., negative in all dilutions.

Case 14.—B. G., aged 14. Admitted to the Episcopal Hospital under the provisional diagnosis of splenomedullary leukemia. Family history, parents living and well. One brother stillborn, one sister died at six months of marasmus. Patient was always delicate and undernourished. Had mumps and pertussis in childhood, typhoid fever at 11. Frequent attacks of sort throat. Complaints on admission, headache, pain in both costal regions, dizziness, constipation, enlargement of abdomen.

Physical Examination.—Pupils, normal. Heart and lungs negative. Liver extends from fourth interspace, midclavicular line, almost to transverse umbilical line. Surface uneven.

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Spleen extends 1 inch below transverse umbilical line and te within ½ inch of a vertical line drawn through umbilicus.

Blood-count: Red blood-cells, 4,600,000; white blood-cells, 7,120; hemoglobin, 44 per cent. Differential: Polymorphonuclears, 66 per cent.; mononuclears, 1 per cent.; transitional, 3 per cent.; lymphocytes, 24 per cent.; eosinophils, 2 per cent. and 4 per cent. of an atypical leukocyte which we were unable to identify. This led to a Wassermann of the blood-serum, which was positive. The patient's father's and mother's blood-serum were then taken and both were found positive, the latter less marked than that of the father or child. The child had a moderate adenopathy, including the epitrochlear gland. Wassermann of serum, still 4 plus after three intravenous, each 0.3 gm. Mixed treatment for six months following; Wassermann of serum then 2 plus. Gain in weight, 38 pounds. Blood-picture normal. Liver normal size. Spleen half the original size. Subjectively well.

TABETIC CASE HISTORIES[1]

CASE 15.—C. T., aged 38. Denies infection. Denies previous treatment. Initial symptoms one year ago were attacks of gastric pain and vomiting. Complains now of ataxia, imperfect control of bladder and bowels, shooting pains in legs, girdle sensation. Is emaciated, has unequal Argyll Robertson pupils. Fundus: gray optic nerves, concentric contraction of all the fields of vision. Ataxic gait. Romberg's sign, positive. Ataxia of left arm. Impaired sensation of left leg. Loss of patellar reflexes. Wassermann of serum, negative; luetin, negative.

Spinal fluid: Cell-count, 50 lymphocytes; Nonné and Noguchi, positive; Fehling's slightly reduced; Wassermann, 0.5, 1.0 and 1.5 c.c. = 4 plus, in all.

CASE 16.—A. B., aged 55. Tabes. Chancre when 22 years old. Took mercury by mouth for six months thereafter. First complained of ataxia four years prior to being seen. Has recently complained of shooting pains in the legs, anesthesia and paresthesia. Imperfect control of bowels. Pupils are dilated, immobile both to light and accommodation. Romberg's sign positive. Impairment of sensation. Ataxia of limbs. Relaxed sphincter ani. Loss of patellar reflexes. Wassermann of serum, 4 plus; luetin, negative.

Spinal fluid: Cell-count, negative; Nonné and Noguchi, negative; Fehling's reduced; Wassermann, 0.2, 0.4 and 0.8 c.c., negative in all dilutions.

CASE 17.—W. A., aged 28. Tabes. Chancre in 1901. Is uncertain as to treatment. Complains only of attacks of gastric pain and vomiting for past year. Is emaciated. Pupils irregular, reacting sluggishly to light. No fundus changes. Romberg's sign suggestive. Sluggish patellar reflexes. Good

1. None of the cases in this group were treated subdurally.

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tone to sphincter ani. Wassermann of serum, 4 plus; luetin, positive (papule and vesicle).

Spinal fluid: Cell-count, 50 lymphocytes; Nonné and Noguchi, very slightly positive; Fehling's reduced; Wassermann, 0.5 c.c. = 3½ plus, 1.0 c.c. and 1.5 c.c. = 4 plus.

Case 18.—M. E., aged 45. Tabes. Charcot's joint. Denies infection and knowledge of any previous treatment. First complaint was of pain and swelling of right ankle four years ago. Paresthesia of lower limbs. Loss of sexual desire, at times diplopia. Is emaciated. Pupils negative. Ataxic gait. Romberg's sign positive. Impairment of sensation in lower limbs. Patellar reflexes absent. Well-defined Charcot's joint right-ankle. Wassermann of serum, 4 plus.

Spinal fluid: Cell-count, 60 lymphocytes; Nonné and Noguchi, positive; Fehling's not reduced, contained blood; Wassermann, 0.2 c.c. plus, 0.4 c.c. 3 plus, 0.8 c.c. 4 plus.

Case 19.—C. M., aged 52. Tabes. Chancre in 1906. Treated with mercury for a short time. Mild secondaries. Complains of weakness in legs and tendency to fall. Is uncertain as to time of onset. Pains in legs, anesthesia and paresthesia. Imperfect control of bladder. Pupils react sluggishly to light. Ataxic gait. Romberg's sign positive. Patellar reflexes absent. Wassermann of serum negative.

Spinal fluid: Cell-count, 250 cells; Nonné positive; Noguchi, slightly positive; Fehling's reduced; Wassermann, 0.5 c.c. negative, 1.0 c.c. ½ plus, 1.5 c.c. 2 plus.

Case 20.—W. B., aged 39. Tabes. Denies infection. Only complaint is shooting pains in legs for past month. Has Argyll Robertson pupils. Beginning optic atrophy. Ataxic gait. Romberg's sign positive. Loss of patellar reflexes. Wassermann of serum, negative; luetin, positive (papule).

Spinal fluid: Cell-count, 30 lymphocytes; Nonné and Noguchi, positive; Fehling's insufficient spinal fluid; Wassermann, 0.5, 1.0 and 1.5 c.c. 4 plus in all.

Case 21.—R. K., aged 57. Tabes. Chancre forty-two years ago. Treated with mercury for about six weeks. Complains of poor vision and at times diplopia for past thirty years. Staggers in the dark. Has unequal Argyll Robertson pupils. Nerve shows atrophic disturbance. Some retinochoroidal changes. Impaired sensation in both legs. Sluggish patellar reflexes. In the Episcopal hospital fifteen years before with typhoid fever. Staggered in the dark and had shooting pains in legs at that time. Dr. G. O. Ring noted Argyll Robertson pupils. Wassermann of serum, negative; luetin, negative.

Spinal fluid: Cell-count, 15 lymphocytes; Nonné, Noguchi, Fehling's, Wassermann, cell-count only made on spinal fluid in this case.

Case 22.—C. B., aged 44. Tabes. Definite history of infection in 1893. Treated with mercury for one month in the secondary stage. First complained in February, 1912, of

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ataxia, failing vision, girdle sensation about the thorax and abdomen, pain and paresthesia in legs. Well nourished. Is unable to stand. Pupils, irregular, react sluggishly to light. Complete optic atrophy. Subsiding neuroretinitis. Lower limbs ataxic, imperfect muscle sense, loss of patellar reflexes. Sphincter ani easily stretched. Priapism recently. He had been a painter but blood showed negative basophilia. Wassermann of serum negative on several occasions; luetin, negative.

Spinal fluid: Cell-count, 80 lymphocytes; Nonné and Noguchi, slightly positive; Fehling's reduced; Wassermann, 0.2, 0.4 and 0.8 c.c., all dilutions negative.

Case 23.—C. H., aged 49. Tabes. Denies infection. First complained of pain in left leg and side, nineteen years ago. Girdle sensation. Hyperphoria. Ataxia. Incontinence of urine. Is emaciated. Marked Romberg's. Ataxic, unable to walk. Unequal Argyll Robertson pupils. Paralysis of third nerve. Has ophthalmoplegia externa. Ataxia of upper limbs. Loss of muscle sense in lower limbs. No patellar reflexes. Sphincter ani easily stretched. Wassermann of serum, 2 plus; luetin, negative.

Spinal fluid: Cell-count, 40 lymphocytes; Nonné and Noguchi, negative; Fehling's reduced; Wassermann, 0.2 c.c. negative, 0.4 c.c. 3 plus, 0.8 c.c. 4 plus.

Case 24.—F. M., aged 55. Tabes. Charcot joint. Chancre thirty-four years ago. Treated with mercury for a short period. First complained of shooting pains in legs three years ago. Developed perforating ulcer of right foot. Charcot joint of left knee which became infected, was amputated above thigh. Has pin-point pupils, no reaction to light. Has necrosis of end of left femur stump. Right patellar reflex absent. Sphincter ani relaxed. Wassermann of serum negative.

Spinal fluid: Cell-count, negative; Nonné and Noguchi, slightly positive; Fehling's reduced; Wassermann, 0.5, 1.0 and 1.5 c.c., all dilutions negative.

Case 25.—S. C., aged 37. Unilateral tabes. Denies all knowledge of primary or secondary lesion. Perfectly well till three and one-half years ago. Sole complaint since then irregular attacks of nausea and vomiting about a month apart. No apparent cause. No pain at any time. Anorexia during attacks. Unconscious of stomach at other times, and appetite then very good. Bowels, regular. Incontinence of urine at times, both day and night.

Physical Examination.—Eyes: right pupil dilated, rigid to light and accommodation; left uninvolved. Face: tremor of tongue and lips and right facial half subject to coarse contraction of muscles, involving malar region and wall of right naris. Very slight ataxia upper extremities. Legs: right knee-jerk absent, left, present. Both Achilles' reflexes absent.

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Slight ataxia. Painless perforating ulcer of left heel. Areas of diminished and dilated pain sense on trunk, ears and feet. Impairment of epicritic sense most marked about ankles. Romberg absent. Hearing unimpaired. Clinical diagnosis confirmed by Dr. Samuel D. Ingham, who believes also that early paresis cannot be ruled out. Gastric analysis was normal.

Nov. 12, 1913: Wassermann of serum, 2 plus.

Spinal fluid: Cell-count, 5; Nonné and Noguchi, slightly positive; Fehling's reduced; Wassermann, 0.2, negative.

Nov. 18, 1913: Repeated because of the incomplete clinical picture. Wassermann of serum, 2 plus.

Spinal fluid: Cell-count, 10; Nonné and Noguchi, slightly positive; Fehling's reduced; Wassermann, 0.6 negative, 0.8 ½ plus, 1.0 1 plus.

This shows very well the advantage of using larger amounts of spinal fluid. Spinal fluid each time under rather considerable pressure. Rectal examination at this time showed relaxation of sphincter ani, stretching causes no pain. No disturbance of sensation over skin of perineum or inner sides of thighs.

Dec. 26, 1913: Patient stated that clinical diagnoses of tabes in an early stage had been made two years prior. No laboratory work was done. One intramuscular of salvarsan given.

Dec. 27, 1913: 0.6 of salvarsan intravenously.

Jan. 3, 1914: 0.6 of salvarsan intravenously.

Jan. 10, 1914: Began sodium cacodylate by hypodermatic injections, and mercuric chlorid by mouth. After 1/10 hypodermatic of sodium cacodylate on Feb. 5, 1914, 0.9 neosalvarsan intravenously.

Feb. 16, 1914: 0.9 neosalvarsan intravenously and in all thirteen hypodermatics of sodium cacodylate, the majority 10 grains to the dose.

March 11, 1914: Wassermann of serum, 3 plus. Spinal fluid, not examined.

It will be noted that the Wassermann of serum has increased under four intravenous injections, which were really provocative. Subsequently used inunctions of 50 per cent. of mercurial ointment.

He is still subject to attacks of nausea and vomiting, though less severe; no longer feels as though walking on cushions, of which he complained at the time of his first visit. All involuntary urination has ceased, both night and day. Pupils, reflexes about the same. Involuntary movements of the facial muscles less marked.

The result of the Abelin reaction in the urine after intravenous 0.6 gm. of salvarsan was negative after two, four and

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six hours; strongly positive after eight hours and negative after ten hours.

TABETIC AND PARETIC CASES WHICH HAVE RECEIVED SUBDURAL TREATMENT, DIRECT OR SWIFT AND ELLIS

CASE 26.—F. P., aged 40. Tabes. Lesion on penis in 1900, another one in 1903. The diagnoses of these were doubtful. Mercury taken for three months. No secondaries. First complaint was failing vision in 1904. At this time had Argyll Robertson pupil, mixed treatment administered. In 1906 had gastric pains, for which at a later period he was operated on. For the past year is ataxic. Losing weight. Imperfect control over bladder and bowels. Sharp shooting pains in the legs. Is emaciated. Ataxic gait. Romberg's sign, positive. Pupils do not react to light or accommodation. Ataxic left leg. Patellar reflexes absent. Relaxed sphincter ani.

Treatment.—Swift and Ellis intraspinal treatment. Neosalvarsan 0.9 gm. was used for the intravenous injections. Forty per cent. of salvarsanized serum, heated to 56 degrees for half an hour, injected intraspinally.

Reaction and Result.—Severe pains in legs, epigastric pain and vomiting after each subdural. Less severe after second. After two injections—patient improved. Rapidly gaining in weight. Ataxia and urinary symptoms greatly improved. Feels subjectively better.

TABLE 1.—RESULT OF ABELIN REACTION IN CASE 26*

	Treatment		
	Before	After	
		First	Second
Blood—			
Luetin	—	—	—
Wassermann	1+	1½+	..
Spinal Fluid—			
Cell-count:			
Lymphos	30	25	10
Polys	..	..	20
Nonné	±?	±	±
Noguchi	±?	±	±
Fehling's	±	±	±
Wassermann in c.c.	0.5, +	0.5, +	0.5, ±
	1.0, 2½+	1.0, 4+	1.0, —
	1.5, 3½†	1.5, 4+	1.5, †

* In this and the following tables ++ = strongly positive, + = positive or Fehling's reduced, ± = slightly positive or slight reduction of Fehling's, ±? = very slightly positive.
† Less than 1+.

CASE 27.—J. K., aged 43. Chancre in 1904. Treated with mercury for the following three months only. Complains of shooting pains and weakness in the legs, and ataxia, gradual in onset, in 1909. Poor vision. Imperfect control of urine. Is emaciated. Marked ataxic gait. Marked Romberg's sign. Absorption of iris in both eyes. Double optic atrophy. Loss of patellar reflexes. No relaxation of sphincter ani.

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Treatment.—Two Swift and Ellis intraspinal treatments administered in the course of one month. Neosalvarsan 0.45 gm. for the intravenous injection, 40 per cent. salvarsanized serum injected intraspinally.

Reaction and Result.—Usual pains in the legs, more severe after first injection. Patient improved. Gait is less ataxic. Walks without the aid of a cane. Better control of urine.

TABLE 2.—RESULT OF ABELIN REACTION IN CASE 27

	Treatment	
	Before First	After First
Blood—		
Luetin*	+	+
Wassermann	4+	..
Spinal Fluid—		
Cell Count:		
Lymphos	20	60
Polys	20	..
Nonné	±	—
Noguchi	±	—
Fehling's	+	+
Wassermann, in c.c.	0.2, —	0.5, —
	0.4, 1+	1.0, 3+
	0.8, 4+	1.5, 4+

*Luetin reaction—marked pustule, same reaction in negative control (*unstimmung Reaktion*).

CASE 28.—J. B., aged 61. Taboparesis. Denies infection. Pains in the legs and arms for the past three years. Now complains of ataxia, anesthesia and paresthesia of the hands and feet, girdle sensation. Imperfect control of the bladder and bowels. Diplopia. Is emaciated. Ataxic gait. Romberg's sign positive. Pupils are unequal, contracted, react to light but not to accommodation. Fundus shows beginning optic atrophy. Ataxia of upper limbs, fine tremor of the fingers of the left hand. Patellar reflex absent. Tremor of the left foot. Relaxed sphincter ani. Very advanced case. Bedridden for some time.

Treatment.—Swift and Ellis intraspinal treatment for four injections; 0.9 gm. of neosalvarsan for the intravenous injections; 40 per cent. salvarsanized serum heated to 56 degrees C. for one-half hour injected intraspinally.

Reaction and Result.—Sharp pains in the legs, vomiting. No improvement noted.

Direct Injection and Final Result.—Two direct injections of 0.01 gm. of neosalvarsan suspended in 10 c.c. of normal salt solution. One intramuscular injection of 0.3 gm. neosalvarsan. No improvement. Marked symptoms of irritation. Less control of the bladder and bowels. Optic atrophy worse.

TABLE 3.—RESULT OF ABELIN REACTION IN CASE 28

		Neosalvarsan	
	Hours	Intravenous	Intramuscular
Urine	48	..	+
Blood	1	+	..
	2	—	..
Spinal fluid	24	..	—

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TABLE 4.—RESULT OF TREATMENT IN CASE 28

	Before		After: Second	Third	Fourth	
*Blood**—						
Spinal Fluid—						
Cell count:						
Lymphos	70		5	30	70	
Polys	3		3	20	..	
Nonné	±		..	..	±	
Noguchi	±		..	..	±	
Fehling's	+		..	..	+	
Wassermann in c.c.	0.1 0.2	++	..	..	0.2 0.4 0.8	++++

* Wassermann 3½ +, Luetin not tested.

CASE 29.—G. M., aged 54. Tabes. Chancre thirty-four years ago. Mercury for a short time. Had moderate secondary symptoms. First symptom fifteen years ago, was shooting pains in the legs. Ataxic gait four years. Girdle sensation. Imperfect control over bladder and bowels. Is emaciated. Argyll Robertson pupil. Marked ataxic gait. Marked Romberg's sign. Disturbed tactile and pain sense in the legs. Muscle sense absent. No patellar reflex. Relaxed sphincter ani.

Treatment.—Swift and Ellis, three weekly injections. Neosalvarsan 0.9 gm. for the intravenous injections; 40 per cent. salvarsanized serum intraspinally. Severe pain in the legs. No improvement was noted.

Direct Injections.—Two treatments, two weeks apart, of 0.015 and 0.01 gm. of neosalvarsan suspended in 12 c.c. of patient's serum and 18 c.c. of normal salt solution.

TABLE 5.—RESULT OF ABELIN REACTION IN CASE 29

	Neosalvarsan: Hours	Intravenous	Intraspinal
Urine	48	..	—
	72	..	—
	96	..	—
Blood	1	+	..
Spinal fluid	24	—	..

TABLE 6.—RESULT OF TREATMENT IN CASE 29

	Before: First	After: Second	Third	Fourth	Fifth
Blood—					
Luetin	—	..	..	..	—
Wassermann	3½+	..	..	..	2+
Spinal Fluid—					
Cell count:					
Lymphos	180	60	44	12	..
Polys	20	..	..	3	..
Endo	1	..	..	..	..
Nonné	—	..	..	..	±
Noguchi	±	..	..	..	±
Fehling's	—	..	..	..	+
Wassermann in c.c.	0.2,— 0.4,— 0.8,—	..	..	..	0.2,— 0.4,— 0.8,—

Reaction and Final Result.—Very severe pain in the legs, retention of urine for a short time. In addition, three intra-

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muscular injections of 0.45 gm. Three intravenous injections of 0.9 gm. No improvement. Marked symptoms of irritation. Leg pains worse. Loss of control over bladder and bowels. Ataxia worse.

CASE 30.—W. McN., aged 51. Chancre twenty-six years ago, no history of secondaries. First complained of anesthesia in the hands five years ago, which later involved the arms and legs. Now complains of ataxia, imperfect control of the bowels, shooting pains in the legs. Is emaciated, markedly ataxic gait, cannot walk or stand alone. Unequal pupils, responding sluggishly to light. Disturbed pain and tactile sensation and ataxia of both arms and legs. Absent reflexes of upper and lower extremities. Good tone to sphincter ani.

Treatment and Result.—Two Swift and Ellis intraspinal treatments. Otherwise treatment and reaction the same as the preceding case, that is, two direct injections. No improvement. Symptoms of irritation not so marked as in the preceding case. Optic atrophy appeared after treatment.

TABLE 7.—RESULT OF ABELIN REACTION IN CASE 30

	Hours	Neosalvarsan Intravenous	Neosalvarsan Intraspinal
Urine	48	..	—
	72	..	—
	96	..	—
Blood	¾	+	..
	1	+	..
Spinal fluid	24	—	..

TABLE 8.—RESULT OF TREATMENT IN CASE 30

	Before	After: Second	After: Third	After: Fourth
Blood—				
Luetin	—	..	..	—
Wassermann	—	..	..	—
Spinal Fluid—				
Cell count—Lymphos	60	36	..	..
Nonné	—	..	..	—
Noguchi	—	..	..	—
Fehling's	+	..	..	+
Wassermann in c.c.	*	..	..	0.2, —
	..	..	..	0.4, —
	..	..	..	0.8, 1½+

* Anticomplementary substance interfered.

CASE 31.—J. K., aged 61. Incipient paresis. Chancre forty years ago. Mercury by mouth for four months. No secondaries. Has had within the last month three epileptiform seizures. Complains also of failing memory, constant headaches. Pupils negative. Slight unsteadiness on turning. Slight Romberg's sign. Patellar reflexes increased by reinforcement. Babinski suspicious, left toe. Tactile and pain sense not impaired.

Treatment.—Two direct injections of 0.01 gm. of neosalvarsan intraspinally, suspended in 12 c.c. of the patient's

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serum and 18 c.c. of normal salt solution. One direct injection of 0.02 gm. of neosalvarsan prepared in the same way.

Reaction and Final Result.—No noteworthy reaction following the injections. Has had two epileptiform attacks during the five months following the injections. Imperfect control over the bladder and bowels. Otherwise no change.

The result of the Abelin reaction in Case 31 was negative in urine, before administration, negative in one, three, six, nine and twelve hours afterward; positive in twenty-four hours, weakly positive in forty-eight hours and negative in seventy-two hours.

TABLE 9.—RESULT IN BLOOD AND SPINAL FLUID IN CASE 31

	Treatment			
	Before	After		
		First	Second	6 Mos.
Blood—				
Luetin*	+	...	...	...
Wassermann	2+	...	...	2½+
Spinal Fluid—				
Cell count:				
Endo	...	20	...	.....
Lymphos	250	300	180	40
Polys	...	20	...	.....
Nonné	—	...	...	+
Noguchi	++	...	...	+
Fehling's	±	...	...	±?
Wassermann in c.c.	0.2, —	...	...	0.5, —
	0.4, ++	...	...	1.0, —
	.....	...	...	1.5, ±

* Luetin reaction delayed—papulopustular.

CASE 32.—W. S., incipient paresis. Denies infection. Epileptiform seizures for the past seven years. Nineteen attacks during the past year. No other complaint. General physical condition is good. Negative findings. Wassermann in blood, positive, + 2.

Treatment.—One intravenous injection of 0.4 gm. of neosalvarsan. Three intramuscular injections of 0.3 gm. One direct intraspinal injection of 0.01 gm. of neosalvarsan, suspended in 12 c.c. of the patient's serum and 18 c.c. of N. S. S.

Reaction and Final Result.—Retention of urine for twenty-four hours occurring three days after the injections. No other reaction. Imperfect control of bladder and bowels. Epileptiform attacks still present.

The result of the Abelin reaction was negative in urine tested at intervals for three days.

CASE 33.—J. D., aged 47. Tabes. Sore on penis twenty-two years before. Disappeared in a few days. No knowledge of secondaries, though he had a sore throat which two physicians regarded as suspiciously luetic. Never took much

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medicine. Occasional sore throat since. Otherwise perfectly well till seven years ago. Then began to suffer from attacks of nausea and vomiting without pain, gradually increasing in severity and at intervals of shorter duration. Occasional fecal and urinary incontinence. Sensory disturbances, hypotonia, pupillary rigidity and myosis. Knee-jerks absent, moderate Romberg, paretic sphincter ani.

Such was his condition March 18, 1914. On two previous occasions, some months ago, he had been given salvarsan. March 22, 1914, the test of blood and spinal fluid resulted as follows: Wassermann in blood, positive; in spinal fluid in c.c. 0.5, 2 —; 1.0, 4 +; 1.5, 4 +. Cell count in spinal fluid, 30 lymphocytes; Nonné and Noguchi positive, Fehling's reduced.

March 28, 1914: 0.9 gm. neosalvarsan given intravenously.

March 29, 1914: 30 c.c. of 40 per cent. serum given subdurally.

March 30, 1914: Temperature rose to 101.8 F., but fell to normal next day, to remain down. Pains in legs—moderate.

April 3 and 4: Repetition of the above procedure. No temperature. Moderate pain in legs.

April 19, 1914: 0.006 neosalvarsan given in 30 c.c. of physiologic salt solution, directly into subdural space. Sharp reaction in a few hours, very severe pains in legs, almost constant nausea, frequent vomiting, retention of urine, obstinate constipation. Catheterization and enemas necessary for three weeks. Absence of epigastric pain altogether with the presence of the autonomic reflex suggested gall-bladder as possible cause of the vomiting; referred to surgical service.

May 5, 1914: Operated on by Dr. W. Wayne Babcock. Gall-bladder thickened, densely adherent to omentum, no stones. Gall-bladder removed.

June 11, 1914: No relief from nausea and vomiting. Has had two attacks since operation. Knee-jerks have returned. Has control of bladder and bowel, though constipated. Romberg, absent. Pupillary phenomena the same. Greatly improved. Laboratory work not repeated.

Case 34.—A. J., aged 52. Paresis. History of infection twelve years ago. Been taking medicine practically ever since. Iritis about six years ago.

TABLE 10.—RESULT OF TEST IN CASE 34

	Treatment	
	Before*	After†
Blood—		
Wassermann	+++	+++
Spinal Fluid—		
Cell count—Lymphos	20	Normal
Nonné	±	+
Noguchi	±	+
Fehling's	+	+
Wassermann in c.c.	0.2 —	0.5, 4 +
	0.4, 4 +	1.0, 4 +
	0.8, 4 +	1.5, 4 +

* Test made Dec. 13, 1913.
† Test made April 1, 1914.

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TABLE 11.—SUMMARY OF REACTIONS*

Method of Neosalvarsan Injection	Patient	Case No.	Gm.	Result: Urine†	Result: Hours	Result: Blood‡	Result: Hours
Intravenous	W. McN.	30	0.9	+	¼	+	1
	G. M.	29	0.9	..	....	+	1
	M. S.	2	0.45	+	3½	+	¼
		..	...	±	5½	+	½
		..	...	—	8	±	1
		..	....	..	....	—	½
	J. K.	27	0.45	..	....	+	½
	J. B.	28	0.9	..	....	+	1
		..	..	..	....	—	2
	P. F.	1	0.9	..	....	—	2
	S. C.	25	0.6	—	2	+	¼
		..	...	—	4	+	½
		..	...	—	6	—	1
		..	...	++	8	—	1½
		..	...	—	10	..	...
Intramuscular	M. S.	2	0.3	±	1	..	...
		..	...	+	3	..	...
		..	...	±	5	..	...
		..	...	+	6	..	...
		..	...	+	12	..	...
		..	...	+	24	..	...
		..	...	±	31	..	...
		..	...	—	33	..	...
	J. B.	28	0.3	+	48	..	...
		30	0.01	—	24	..	...
Intraspinal	W. McM	..	...	—	48	..	...
		..	...	—	72	..	...
	G. M.	29	0.015	—	12	..	...
		..	...	—	36	..	...
		..	...	—	72	..	...
	W. S.	32	0.01	—	2	..	...
		..	...	—	8	..	...
		..	...	—	12	..	...
		..	...	—	24	..	...
		..	...	—	36	..	...
		..	...	—	48	..	...
		..	...	—	72	..	...
	J. K.	31	0.01	—	1	..	...
		..	...	—	2	..	...
		..	...	—	5½	..	...
		..	...	—	9	..	...
		..	...	+	12	..	...
		..	...	±	48	..	...
		..	0.02	—	2	..	...
		..	...	—	6	..	...
		..	...	—	48	..	...
		..	...	—	72	..	...

* Spinal fluid tested only in Case of W. McN. Result, negative after twenty-four hours.

† Control, specimen of urine voided just before the injection of neosalvarsan was tested.

‡ Control, specimen of urine free of neosalvarsan was tested. An unsuccessful attempt made by means of the Abelin reaction to determine whether any of the neosalvarsan was taken up by the erythrocytes or whether all of it goes into the serum.

Dec. 10, 1913: Homicidal and suicidal mania. Facial spasms. Speech thick, inarticulate at times. Suspicious, ungovernable appetite. Has insomnia. Lost memory. Cannot be trusted alone, no longer able to read. Unequal pupils, react to light and accommodation. Knee-jerks prompt. No

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Babinski or clonus. No relaxation of sphincter ani. Perfect control of bladder and bowel. Tremor.

Dec. 16, 1913, test was made on blood and spinal fluid.

After Dec. 16. 1913, he was given seven intravenous injections of 0.9 gm. neosalvarsan at weekly intervals, then three hypodermatic injections each week, each of sodium cacodylate, 15 grains.

Result.—Clinical improvement, none. Laboratory studies: Serum, unchanged, + + +. Spinal fluid unchanged as to Wassermann, cell-count fell to normal.

April 10, 1914: Subdural injection 30 c.c. of 40 per cent. neosalvarsanized serum. No reaction.

April 17, 1914: Subdural injection, direct, 0.008 of neosalvarsan in salt solution. Sharp reaction in a few hours, pain in hips and legs, vomiting which continued for two days, retention of urine necessitating use of catheter for twenty-four hours.

Final Result.—Gradual improvement. Mind now clear, memory good, reads paper and discusses topics, tremor almost nil, speech greatly improved. Pupillary phenomena unchanged.

We wish to take this opportunity of thanking Dr. Noguchi for the luetin which he kindly sent us and which we have used in over 100 cases of syphilis; also Dr. E. G. Alexander, chief of the Genito-Urinary Dispensary of the Episcopal Hospital, who permitted us to draw on his service for some of the cases studied.

327 South Seventeenth Street.—Protestant Episcopal Hospital.

ABSTRACT OF DISCUSSION

Dr. Edward L. Tuohy, Duluth, Minn.: Did Dr. Robertson find, in his experience, any marked evidences of difference in the various forms of this disease. It is said that in the Orient syphilis is more severe than in civilized countries. It is also said that it is more prone to attack the central nervous system. There happens to be a tremendous amount of discussion regarding the many heart-lesions that occur in lues and I would ask why this is. In tuberculosis we realize that when once an individual is tuberculous he is always tuberculous. It is shown that tuberculosis originates, as a rule, in childhood and such an individual will remain tuberculous thirty or forty years after inoculation. The same thing applies to lues; when once inoculated the individual remains syphilitic throughout his life. Regardless of all treatment the spirochete remains in the tissues until the end of the man's life. In the course of time, for some unknown cause, special predilection is manifested for some

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particular organ or tissue, after a period of apparent latency. In some instances this latency is so well concealed that only a Wassermann test will reveal it. The spirochetes lodge here and there in the body and the central nervous system is frequently involved. Often the "hit and miss" treatment may do good, but, on the other hand, may do harm by upsetting the immunizing processes that the body has developed.

Dr. B. F. Diseroad, Philadelphia: Will Dr. Robertson explain the following condition and state if in his experience he has made the same observation? We find a number of individuals with syphilis of long standing who give a history of chancre twenty or twenty-five years previously. This is followed by a long period of latency with the individual apparently enjoying good health, when suddenly manifestations of the disease crop out, either as tubercle syphilids, gumma of the internal organs and superficial structures, or of the central nervous system. Why then do these tertiary lesions following this latency occur singly in one of these various locations? All of these patients not treated for syphilis developed symptoms indicating lesions in cord or central nervous system. Some years ago I treated an elderly person who gave a history of recent trauma, but no history of any initial lesion. In the limb injured a gumma developed, but a clinical diagnosis was not made until symptoms of a lesion of the central nervous system cropped out, which was proved by a 4-plus Wassermann. Salvarsan caused an arrest of symptoms and the gumma promptly disappeared.

Dr. A. J. Caffrey, Milwaukee, Wis.: I think Dr. Robertson is wise in bringing out the point concerning the elimination of the primary chancre in syphilis. I know of a surgeon in Milwaukee who punctured his index finger while circumcising a primary chancre. No chancre appeared as a result but the secondary symptoms of syphilis appeared after a few weeks. He went on to an advanced paresis from which he died. Evidently this was a case in which the man became infected at the time of the circumcision without the appearance of a chancre. Dr. Lorenz of the state insane asylum at Madison, Wis., reported some success in the treatment of these cases, at a meeting of the Wisconsin State Medical Society in Milwaukee. He gave neosalvarsan in minute doses —not by the Swift and Ellis method but by direct intradural injections.

Dr. J. V. Klauder, Philadelphia: In a study of the cerebrospinal fluid from syphilitic patients, in a series of cases greater in number than those given by Dr. Robertson, the following results were obtained. Our list of cases does not include any of primary syphilis. In 70 per cent. of patients with secondary syphilis, we obtained some evidence of an abnormality of the cerebrospinal fluid. Ravaut gives 67 per

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cent.; Dreyfus 80 per cent. In our series of tabetic cases we obtained a positive Wassermann in the serum in 62 per cent. of the cases. Swift and Ellis and Hauftmann both report 66 per cent. The Wassermann in the spinal fluid in the same series was positive in 82 per cent. of our cases, and Swift and Ellis report 87 per cent. The spinal fluid in all of our tabetic cases showed some evidence of an abnormality, except one, a clear-cut case, in which the spinal fluid was normal. In the same series, about one-half either denied infection or had mild secondaries. Attention has already been called to this, especially by Mott. Many of the tabetics gave a history of what was no doubt mixed infection; I believe this occurrence of mixed infection is more common than is usually accepted. The published reports of the intraspinal treatment of tabes and paresis are somewhat contradictory. The literature on this subject is rather confusing. Many do not countenance subdural injections of any character in the treatment of lues. In the Swift and Ellis treatment the dose of salvarsan or neosalvarsan contained in the serum is indefinite and variable. In the direct intraspinal treatment Ravaut advocates the injection of a rather large amount of salvarsan in a hypertonic salt solution, as much as 12 mg. Marked symptoms of irritation following this plan of treatment have been reported. We have injected 20 mg. of neosalvarsan intraspinally, which was followed by marked symptoms of irritation, in some cases. We do not believe that the efficiency of the treatment depends on the large dose injected. Ogilvie advocates the direct intraspinal injection of neosalvarsan in small amounts not exceeding 1 mg. No definite plan of direct intraspinal treatment has yet been formulated. The Swift and Ellis technic is a matter still *sub judice*. We believe that the most accurate plan so far as dosage is concerned, is first, to remove some of the patient's serum, following this by an intravenous injection of the dosage decided on, and, finally, to introduce into the inactivated serum a definite amount of neosalvarsan not exceeding 5 mg., which should be given subdurally. This method also possesses the advantage of saving considerable time, and permits the treatment of several cases in the time usually allotted for one Swift and Ellis treatment.

Dr. W. W. Tompkins, Charleston, W. Va.: What observations have been made in treating cases of syphilis of benign character as found in the negro? Of the negroes in my community many are intemperate, ignorant, suspicious, and will not carry out any directions given them in the way of treatment. If they come with a chancre one can do practically nothing after making the diagnosis. When the secondaries appear it is difficult to make them out because of the color. There is one point of

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interest, however, with regard to the occurrence of syphilis in the negro. I have observed that certain glands become enlarged, but the patients go on from year to year and do not suffer from the disease. So far as the late symptoms of the disease are concerned, such as locomotor ataxia and paresis, they are the rarest things in the world among the negroes. The glands that become infected are the cervical; they enlarge and after awhile they suppurate, then heal, leaving scar-tissue with more or less deformity. The surprising thing about these cases is that, with little or no treatment and in a class of patients that are often underfed and overstimulated, the symptoms should be so mild and free from serious complications or sequelae.

Dr. W. E. Robertson, Philadelphia: I have had little experience with lues in the colored race, so that I am unable to state whether or not grave lesions are common among negroes. In a few instances I have seen optic atrophy, tabes and other evidence of profound involvement of the nervous system in the negro, and such cases I believe are fairly frequent in the wards of the Philadelphia General Hospital. Concerning the modern treatment of luetic infections, we feel forced to utter a note of warning. The rapidity with which primary and secondary lesions disappear after an initial intravenous injection gives a false sense of security to the patient and increases the moral obligation of the physician. Unless he makes clear the necessity for careful laboratory studies, both for diagnostic purposes and as a guide to treatment, there will probably be many more tertiary and paraluetic (so-called) wrecks than confront him now, as a result of the mercury and iodid plan of treatment. Consistently treated, both intravenously and with mercury in some form, it is probable that every patient would make a complete recovery; neglected it is still problematic how large a proportion can be saved by subdural therapy. We feel certain that no one in whom sequential exudation and inflammation has occurred can hope for much from any form of treatment. We also believe that when subdural treatment is practiced the dose injected should not exceed 5 mg. and as the dosage under the Swift and Ellis plan must be speculative, it would seem better first to remove the patient's serum, separate and inactivate it, then prepare the intravenous injection, removing an amount not exceeding 5 mg., which should then be injected in the subdural space after diluting it in the previously inactivated serum. The rest of the salvarsan solution should then be given intravenously.

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BLOOD TRANSFUSION BY THE SYRINGE CANNULA SYSTEM

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NEW YORK

The time allowed for a paper under the present circumstances will not permit of a full discussion of the subject in hand. I therefore omitted a summary of the literature, the excellent work of others in this field, problems of technic, questions of accidents, etc. I will confine myself to some of the principles involved in blood transfusion and speak of some of its applications.

When one considers the many facts about the blood, not generally recognized, which are known, and the many facts yet to be learned, one cannot help but realize the complexity of this tissue. Many diseases produce changes in quantity and quality of the blood. Changes in quantity and quality of the blood are responsible for many pathologic conditions. Failure on the part of the blood to modify its quality properly and adequately to meet the required demands in the various conditions is frequently responsible for the existence of disease, especially infections. It is only by a thorough study of this complex tissue in the normal and by a study of this tissue under pathologic conditions that one may obtain a clear conception of the possibilities of blood therapy. Further studies of the mode of operation of substances and elements of the blood in disease will perhaps suggest to us possibilities in modifying the blood of a donor or patient to meet the needs of the case and make more potent the agencies involved in overcoming disease. These studies are necessary not only that we

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may know when and how to apply blood therapy but equally important that we may know when not and why not to employ it.

Permit me to take up with you some of the conditions in which blood transfusion therapy may be considered.

Aplastic Anemia.—A disease usually of young adults, short, febrile course and always fatal. The anemia is progressive with no remissions of the disease, and the termination is usually in hemorrhage. In this disease leukoblastic and erythroblastic activity becomes completely and permanently paralyzed. The introduction of fresh blood is wholly inadequate to modify favorably the course of the disease. This statement is based on three cases in my own experience with a support of the literature among the reliable authors.

Splenic Anemia with Hematemesis.—In this group we may for our purposes include Banti's disease. In many cases syphilis plays a prominent rôle. Where syphilis prevails and the anemia is in excess of the blood lost, transfusion will be of little aid until the patient has received antisyphilitic treatment (case report[1]). After receiving such treatment, transfusion in severe cases is specific. Following the combined therapy splenectomy deserves respectful consideration.

Gastric Ulcer with Hemorrhage and Anemia.—In traumatic hemorrhage or hemorrhage from ulcer, nature provides two factors of safety in checking it: (1) a fall in blood-pressure, and (2) a decrease in coagulation time. The decrease in coagulation time is brought about by dilution of the blood with fluid of the tissue. This fluid carries with it tissue extract. Tissue extract reduces coagulation time. If transfusion be contemplated it should preferably be done after all bleeding has ceased, and a sufficient

1. Lindeman, Edward: Blood Transfusion, THE JOURNAL A. M. A., March 28, 1914, p. 993.

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time allowed for a crust to seal over the bleeding area. If both operation and transfusion be done, transfusion should preferably be done first whether the patient is actively bleeding or not. Anesthesia and operation should immediately follow. The patient will bear the anesthesia well, the shock of operation will be prevented; sensory and other reactions which occasionally follow transfusion never become manifest, and a poor surgical risk is converted into a good one. My experience is that when the hemorrhage is profuse and several occur within twenty-four or thirty-six hours, the ulcer is likely to be a deep one. These are naturally more liable to perforate. In these cases transfusion and operation should be done without delay.

The treatment of severe hemorrhage by blood transfusion is specific. The results when proper transplantation is accomplished are nothing short of brilliant.

Alcoholic Cirrhosis of the Liver with Severe Secondary Anemia.—The liver cirrhosis is no contraindication. The results are good. Ascites may follow transfusion, but this ascites clears up later. My patients have all done well even when syphilis was associated. In liver disease Whipple found a diminution in the fibrinogen of the blood. The purpuric eruption and also hemorrhage which not infrequently accompany the disease may thus in a measure be easily accounted for. Where varicosities of veins prevail both factors may be operative in causing hemorrhage and anemia. Hence the rational procedure for the relief of the condition is the transfusion of whole blood.

Acute Leukemias.—I have had no success in the treatment of this disease, in either the proliferative or destructive forms, with or without hemorrhage.

Hemophilia.—A family disease following the law of Nasa. Here we encounter a condition of the blood which permits of a greatly delayed coagulation time,

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the blood failing to clot in over one hour. In the circulating blood fibrinogen, calcium salts, prothrombin and antithrombin are constant constituents. Antithrombin holds the prothrombin in combination and prevents its conversion or activation into thrombin. When blood is shed the disintegration of platelets furnishes material called thromboplastin which combines with the antithrombin and the prothrombin is liberated. Prothrombin freed is rapidly changed to thrombin and in the presence of calcium salts converts fibrinogen into fibrin (Howell). From the most recent researches of Howell in hemophilia, the condition is associated with a decrease of prothrombin which necessarily means a relative increase of antithrombin. In this disease two conditions are corrected by blood transfusion: (1) prothrombin is supplied; (2) the lost blood is replaced. Human blood-serum in sufficient quantities will supply enough prothrombin to stop the bleeding. Blood-serum will not replace the formed elements of the blood lost. Hence, in severe cases blood transfusion is the measure of choice and should be performed during the active stage of bleeding. In some cases it might be considered as a prophylactic after all bleeding has ceased. After transfusion the coagulation time is materially reduced but, curiously enough, does not remain constant. A case may illustrate this point:

A typical case in the series of Dr. W. Gilman Thompson, Bellevue Hospital, in a man, aged 29, with multiple hematoma in joints, loose tissues of the neck and floor of the mouth. His life was endangered by strangulation. May 22, coagulation time over 45 minutes; May 23, 230 c.c. was transfused; May 24, coagulation time 17 minutes; May 25, coagulation time 19 minutes; May 25 200 c.c. was transfused; May 28, coagulation time 12 minutes; May 29, coagulation time 14 minutes; May 30, coagulation time 15 minutes; June 2, 200 c.c. was transfused; June 4, coagulation time 8 minutes 10 seconds. Patient had no recurrence of bleeding since the second transfusion until one year later, when he came to my office with a hematoma of the left wrist. His coagulation time was then a little over one hour when an imperfect clot had formed. He was then transfused again with good

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result. Dr. Crile, in a personal talk, informed me that some of the cases in his experience remained in a normal condition for several years after treatment.

Simple Anemia of Grave Degree of Unknown Cause.—Most common in girls and young women between 10 and 20 years of age, frequently fatal. The coagulation time is slightly delayed, menstruation is irregular and at times a little excessive. Epistaxis is occasional. The anemia is frequently fatal and yet shows none of the characters of pernicious or aplastic anemia or hemophilia. In cases in which the usual forms of treatment have been exhausted with no improvement, striking results are obtained with blood transfusion. After overcoming some of the anemia by blood transfusion, the patient, who has previously shown no hematopoietic function, begins to make new blood. However, the anemia must be overcome to a considerable degree before the patient is capable of blood regeneration. Not only does the new blood correct the pathologic condition in part but, apparently stimulates hematopoiesis. We may well apply here the maxim, *Ex nihilo nihil fit,* "Nothing can be made out of nothing." This stimulation is probably due to the increased nutritional condition of the hematopoietic organs themselves, which nutriment furnishes material from which new blood may be made. Once the patient assumes good hematopoietic activity the road to recovery is rapid and cure is complete.

Postoperative Cholecystotomy (where bleeding from the wound cannot be controlled).—Human serum in large quantities may help. In some cases, however, this may not help and transfusion of blood is necessary. In severe cases it may be necessary to transfuse every day or every other day or every three or four days according to the variation in coagulation time and variations in the blood lost. If the patient's blood coagulation time is maintained within eight minutes all bleeding will cease; but at this point the

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patient remains at a low level of safety. Hence, though bleeding has ceased, a lower coagulation time should be aimed for. A severe anemia from preceding illness may be present and a relatively small hemorrhage can produce grave symptoms. Whole blood adequately satisfies all the necessary needs of the case. According to Falta, also King, bile pigments have considerable affinity for calcium; when the pigments appear in the circulation the heart muscle rapidly gives up some of its calcium. In consequence the heart action is impaired. In this condition, as well as in some cases of pernicious anemia, I usually use Locke's modified Ringer's solution, without the dextrose, for improving, if possible, this cardiac tone. The solution is used in place of saline.

Carcinoma and Sarcoma.—The fact that malignancy is common in some families and absent in others, and the fact that tumors are not transplantable in all individuals of a species, would lead one to conjecture the possibility that inhibitory substances may be present in some individuals and that these substances reside in the blood. Crile has reported a cure of sarcoma in a dog by blood transfusion from an immune animal. In my experience thus far I have no evidence one way or another. The operative risk, as in many other conditions, is undoubtedly diminished by blood transfusion.

Malnutrition.—The life of a starving animal cannot be maintained by the transfusion of blood from a normal, well-fed animal. The bulk of the energy represented in the blood is in a potential form. That which is kinetic is relatively small. Hence, one cannot hope for much in cases of malnutrition in infants. I have had a little success in this field, but I feel that what virtue it may possess must lie in its stimulating quality. Of course, when anemia is associated, the results in some cases should be good. In the majority of cases of malnutrition in infants, in spite of the pallor and emaciation, the red cells and

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hemoglobin approach very close to normal, sometimes even higher. This is a little difficult to understand. There may be a reduction in volume of the blood due to dehydration of the tissues, and the anemia may be masked by concentration. This, however, is a theoretical point, and deserves no place here.

Purpura Hemorrhagica.—The condition may be primary, or may be secondary to some accompanying or preexisting disease. We may divide them conveniently for our purposes into four groups: (1) cases associated with diminution of platelets; (2) cases associated with diminution of fibrinogen; (3) cases associated with diminution of prothrombin; (4) all other cases.

Groups 1, 2 and 3 are either improved or cured by blood transfusion. As to Group 4, the condition or course of the disease in many of the cases in this group is not modified.

Sepsis.—I must here cite one case, a patient referred to me through the kindness of Dr. F. S. Meara of New York:

A. H., aged 11 years. Diagnosis: Rheumatic fever with malignant endocarditis. Child is very ill, emaciated, very weak, anemic; hemorrhagic mucous membranes; petechiae on skin and blood in stools. Systolic murmur of mitral insufficiency; liver and spleen just at the level of umbilicus, and some edema of extremities. For the past eighteen months child has been ill with the following diseases in succeeding order: asthma, tonsillitis, rheumatic fever, bronchopneumonia, diphtheria, otitis media, mastoiditis with involvement of sphenoid bone, and is now suffering with the disease mentioned above. In spite of repeated negative blood-cultures, it was felt that the child had a blood infection, from some obscure focus, probably the heart valves.

July 18, 1913: Strong positive complement fixation test to *Strepococcus viridans* (Research Laboratory, Department of Health, New York); 280 c.c. of blood was transfused in median basilic vein from father. Time three minutes. One hour later temperature 101 F.; normal in evening.

August 1: Second transfusion; 360 c.c. of blood was transfused from father. Time from beginning to end of operation twelve minutes. No reaction.

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August 8: Third transfusion; 260 c.c. of blood was transfused from father. No reaction. Mastoid wound previously showed little tendency to heal, but now shows increased granulations and decreased discharge.

August 15: Fourth transfusion; 220 c.c. of blood was transfused from father. No reaction.

August 21: Red blood-cells, 2,700,000; hemoglobin, 70 per cent.

August 22: Fifth transfusion; 260 c.c. of blood was transfused from father. Fifteen minutes later there was a slight general urticaria. After this transfusion child made rapid progress in strength and increase in appetite.

August 29: Sixth transfusion; 280 c.c. of blood were transfused from father. Fifteen minutes after this transfusion child developed a general urticaria. First transfusion was followed by chills and slight temperature. No chills and no rise of temperature followed the succeeding transfusions.

September 5: Child began to go out in an automobile daily. Her course has been one of continuous progress ever since. Convalescence dates from August 29, the day of the last transfusion.

November 22: Child is now practically well save for occasional attacks of asthma for which she is sent to a warmer climate.

December 1: Condition good.

Aug. 1, 1914: Condition excellent. Child weighs 90 pounds. No recurrence of the disease.

In the analysis of the case of A. H., and in the explanation of the successful results obtained, I desire to advance the following statements which I present in the form of a theory:

In this case it might be said that three prominent conditions prevailed:

1. Chronic sepsis.

2. A severe anemia secondary to sepsis.

3. Multiple purpuric hemorrhages secondary to sepsis.

[From observations in this case and from observations in nine other cases of chronic sepsis, I am convinced that blood of a normal healthy individual contains bactericidal elements or elements that inhibit bacterial growth, that possess considerable potency. These elements when introduced convey some degree of passive immunity.

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THEORY

"This immunity follows the law of passive immunity and is greatest at the time of introduction of blood, and gradually disappears with time either by elimination or modification. If this be true the introduction of fresh blood will inhibit septic processes for a time at least until the bactericidal or inhibition substances introduced become impotent. At this point bacteria may assume their previous activity and the condition is unrelieved. However, if blood is introduced repeatedly, this bacterial activity will be checked in part.

The parallelism of anemia and low resistance to infection is a well-known fact.

When a sepsis produces an anemia a vicious cycle presents which prevents the host from developing active immunization to the infection.

If we assume a certain threshold necessary in the host, in terms of red blood-cells and hemoglobin for the production of an active immunity, then repeated transfusions will check septic processes and overcome the anemia to a degree that will enable the host to develop his own active immunization which will destroy the organism causing the disease."]

It takes more than one swallow to make a summer. And, in support of my contention I have had nine other cases of sepsis in which there were two deaths. In one case in which death occurred a child of 6 years had appendix abscess and spreading peritonitis and gangrene of the cheek. In the other case a man aged 39 had a streptococcus septicemia. The blood culture yielded 200 colonies per 3 c.c. of blood. These cases will be published in detail elsewhere. The literature of many experimental workers would seem to bear out this contention. Von Behring, Fodor, Nuttal, Nissen, Buchner, all showed that fresh normal blood and blood serum will kill bacteria in a reagent glass. Lemaire and also Buxton found that after the infection of pathogenic micro-organisms directly into the

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circulation there is first a reduction in their number followed later by an increase. It is supposed that the natural antibactericidal forces of the serum and leukocytes take up the destruction of the bacteria until the former are exhausted, and from this time proliferation will take place without hindrance. In typhoid infection it would seem that the first organisms which reach the circulation are killed. In this destruction there is a great loss of bactericidal agencies, so that continued invasion results in general infection. Evidence is abundant that the blood is endowed with a natural protection against the invasion of bacteria, and in most of us it is only when infected by an organism of high virulence that we are overwhelmed. If, however, by the removal of the natural immune substances through long illness, alcoholism, bad habits, etc., an individual may be wholly incapable of warding off infection, even of low grade virulence, and chronic sepsis may easily ensue. The increased bactericidal power of the serum which develops in immunization or infection is an index of the increased resistance of the individual against infection. If this be true the reverse must be true, and where there is no bactericidal power in the blood there is no resistance to infection. In streptococcus and staphylococcus infections, protective serums have been obtained in laboratory animals, but the quantity required for use in man at the present time precludes the possibility of application. The defense of the body against streptococci depends on the power of the leukocytes as well as the opsonin and other bactericidal substances of the serum. Hence the bactericidal power *in toto* resides in the whole blood.

40 East Forty-First Street.

ABSTRACT OF DISCUSSION

Dr. G. M. Dorrance, Philadelphia: The published results from transfusion in pernicious anemia, and my own results agree with them, have not been favorable in cases in which only one transfusion of a large amount is performed. Excep-

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tional cases of course occur. We have had two cases of cure, both in young subjects, and several cases in which transfusion was successful in the first instance but was followed by death several months later. The syringe method of which Dr. Lindeman is an advocate seems to be destined to supersede the direct connection between artery and vein and from vein to vein. This method has been used for several years by Drs. Cooley, Edwards and others, the difference being that they use a larger syringe. We have not had experience in the treatment of chronic infections by frequent transfusions, but in acute infections the use of blood-serum or one large transfusion has not altered the course of the disease in any of our cases. In most melena cases, serum, foreign or human, usually controls the bleeding. In a few very severe cases transfusion is indicated. Too much care cannot be exercised in the selection of the donor in order to rule out syphilis, tuberculosis, etc.

Dr. S. Adolphus Knopf, New York: Will Dr. Lindeman tell us what has been his experience with tuberculosis cases and how the patients felt after transfusion?

Dr. A. E. Jaffin, Jersey City: Five years ago I transfused a patient with pernicious anemia by the cannula method, and although the patient died three days later the hemoglobin rose 20 per cent. Coincident with this rise in hemoglobin there was cardiac distress that stopped us from going higher. As an intern I recall cases of malignant endocarditis that were repeatedly transfused shortly after Dr. Crile had revived the subject. The success we had then was not as marked as Dr. Lindeman's now. In one case there was a streptococcus invasion of the mitral valve.

Dr. E. Lindeman, New York: In the technic, specially devised cannulas are painlessly inserted into veins of the donor and patient, without skin incision. About 15 syringes are employed. No syringe is used a second time until thoroughly cleansed. One operator manages the syringe of the donor, another that of the patient. One syringe is being filled while another is being emptied. A little saline is allowed to trickle through the patient's cannula every now and then to prevent the possibility of any coagulation in the cannulas. The syringes are passed from donor to patient in rapid succession until the desired quantity of blood has been transfused. The system thus operates as an artificial human heart. It requires from six to twelve seconds to fill and empty a syringe. The largest quantity I have taken from one donor in one sitting is 1,500 c.c.; the time required was fifteen minutes; 30 c.c of saline was used. The coagulation time of blood carefully drawn into a syringe is never less than five minutes. Hence, no change can take place in the blood during the transfer, for the entire blood-mass, regardless of the amount, is outside the

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human body for a period of less than twelve seconds. In speaking of sepsis, I tried to emphasize the fact that we have, in the circulating blood of normal healthy persons, natural bactericidal substances more powerful than any substances in the pharmacopeia at present capable of being injected into the circulation for the treatment of many infections. Undoubtedly, the degree of natural immunity will vary with many persons, as Dr. Park has shown in the protection from diphtheria; some possess it, others do not. In the selection of donors, those who have proved successful in septic cases are used for similar cases. For the treatment of typhoid fever donors are kept immunized during the typhoid fever season. In answer to Dr. Knopf's query concerning transfusion in tuberculosis, I must beg to decline to make a statement at present. The work is being pushed as rapidly as possible and a report will follow in due time. I have purposely omitted the subject of pernicious anemia, yet there is perhaps no disease that presents itself more frequently to one engaged in the field of blood therapy. Cases referred to me from time to time now make a large series. These have been subjected to a critical analytic study. Because there is so much to be said on this subject I have preferred not to enter on it at this time. When the patient, however, has reached a critical condition, when all other forms of treatment have been exhausted, there is no therapeutic measure known that has any parallel in efficacy in robbing the disease of much of its terrors as blood transfusion when properly applied.

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A STUDY OF DIFFERENT NITROGENOUS DIETS IN CHRONIC NEPHRITIS *

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The object of this study has been to note the effect of diets containing different amounts of nitrogen on cases of chronic nephritis. To study this effect, attention has been paid especially to the different tests devised in recent years to show renal function, to the blood-pressure, and to the general condition of the patient.

Many articles have appeared in medical literature concerning the value and effects of different types of diets in chronic nephritis. No attempt will be made to review those articles which deal with the effect of diets on the general condition of the patient, nor shall we take up the literature which deals with the effect of diets in which other food elements than the nitrogen have been varied. In a study on nephritis in 1905 Widal[1] and Javal among other points showed that the urea of the blood became elevated in certain types of chronic nephritis when increased nitrogen in the food was consumed, or when urea was added to the diet. In 1913 Goodall[2] declared that the blood-pressure fell in chronic nephritis when the patients were placed on a low protein diet. In one case he found the non-protein nitrogen of the blood low after the low diet, and concluded that the general condition and blood-pressure were dependent on the presence of the end-products of protein metabolism in the blood. Seymour[3] in 1913, and Folin, Denis and Seymour[4] in 1914 reported on cases of chronic nephritis given diets

* From the Department of Medicine, Harvard University, and the Medical Clinic of the Peter Bent Brigham Hospital.

1. Widal: La Semaine méd., 1905, xxv, 313.
2. Goodall: Boston Med. and Surg. Jour., 1913, clxviii, 761.
3. Seymour: Boston Med. and Surg. Jour., 1913, clxix, 795.
4. Folin, Otto, Denis, W., and Seymour, Malcolm: The Non-Protein Nitrogenous Constituents of the Blood in Chronic Vascular Nephritis (Arteriosclerosis) as Influenced by the Level of Protein Metabolism, THE ARCHIVES INT. MED., 1914, xiii, 224.

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containing average, high and low amounts of protein. No accurate record was mentioned of the amount of the diet refused by the patient. They found that the patients on the high diet did not seem so well, and that the non-protein nitrogen of the blood could be increased or lowered by the diet. They found no relation between the blood-pressure and the nitrogen retention and no relation between the phenolsulphonephthalein elimination and the non-protein nitrogen of the blood when the latter was varied by the diet.

The numerous observations from which this paper is compiled were made for the most part by one or the other of us. In some instances, however, the records of the Peter Bent Brigham Hospital were used. During the time the work was in progress frequent comparisons were made between our figures and those of the hospital physicians, so that we feel no hesitancy in using their figures when it is necessary.

Any one who has worked on a problem quantitatively in a general hospital will realize the possibilities of error that readily creep in. Careful supervision of the work in these experiments makes us feel that although an occasional error may have produced some unexpected result, the figures as a whole are relatively accurate. Of course, we should not draw any conclusions from a single observation in this kind of work.

For these studies three different types of diets were selected. They all contained as nearly as possible the same number of calories and the same amount of sodium chlorid. In addition to the salt in the food enough was added in the cooking to bring the total up to approximately 4 gm. a day in each diet. One diet, called the standard nephritic diet, contained about 73 gm. of protein daily. Another, called the high protein contained about 149 gm. of protein daily, and the third, called the low protein diet, contained about 26 gm. of protein daily.

For our estimations it was assumed that if the amount of protein was divided by 6.5 the result would show the number of grams of nitrogen. Thus the high protein diet contained practically 23 gm. of nitrogen, the standard diet 11.2 gm., and the low protein about 4 gm. of nitrogen daily.

The hospital dietitian, Miss McCollough, spent considerable time in endeavoring to make up meals which contained these amounts of protein and sodium chlorid in the twenty-four hours, and which would be palatable and variable from day to day. We take pleasure in this

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opportunity to extend to her our thanks. The figures for values of raw food were taken from the United States government bulletin, for cooked food from Locke's[5] tables. In the high protein diet it was necessary to increase the caloric value from the usual 2,100 to 2,600 in order to make the meals palatable.

As many of the studies could not be carried out completely owing to the patients leaving the hospital or to other causes, we shall have to report some cases in which only certain points have been brought out. The plan followed when possible consisted in letting the patient rest for a few days after entrance to the hospital on a simple light diet. After the patient had become used to the new surroundings, the standard nephritic diet was started and an accurate record kept of the amount of protein eaten at each meal. While the patient was on the standard nephritic diet, on one day 10 gm. of sodium chlorid, on another 20 gm. of urea were added to the diet, in order to study the ability of the kidneys to excrete those substances. Widel[6] has divided nephritis recently into those cases which are unable primarily to excrete sodium chlorid and those that are unable to excrete non-protein nitrogen. Schlayer[7] and Monakow[8] have suggested the foregoing two tests to show the kidneys' ability in regard to salt and nitrogen.

After the patient had been on the standard nephritic diet for a few days the amount of non-protein nitrogen in the blood was determined and the phenolsulphonephthalein excretion test done. The patient then was placed on the high protein diet for a few days and these two tests repeated, then on the low protein diet for a similar period and the tests were done again. The amount of fluid intake and output was recorded as was also the specific gravity of the urine. The amount of nitrogen and salt excretion during many of the experiments was studied throughout, while in others only in part. Blood-pressure observations were made from time to time.

The amount of the non-protein nitrogen in the blood and the power to excrete phenolsulphonephthalein were taken as the two most comprehensive single tests for renal function at the present time. Recent work on these tests by us[9] has shown that the two tests in general

5. Locke: Food Values, D. Appleton & Co., 1911.
6. Widal: Mouvement méd., 1913, i, 1.
7. Schlayer and Takayasu: Deutsch. Arch. f. klin. Med., 1910-1911, cl, 333.
8. Monakow: Deutsch. Arch. f. klin. Med., 1911, cii, 248.
9. Frothingham and Smillie: The Archives Int. Med., 1914, xiv, 541.

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parallel each other, although there may be considerable variation in the phenolsulphonephthalein excretion because of passive congestion or other unknown causes, in cases in which the blood nitrogen remains constant. Our feeling is that the amount of non-protein nitrogen in the blood is slightly the more reliable test of the two. By the methods used for determinations the normal amount of non-protein nitrogen in the blood is between 20 and 30 mg. per hundred c.c. The normal excretion of phenolsulphonephthalein in two hours is more variable, but roughly from 50 to 70 per cent.

The following methods were used for making the different determinations, and references are given to the description of the technic by the originators of the tests. As no modifications were employed, we shall not give a description of the technic. For determinations of the non-protein nitrogen of the blood we used the Folin and Denis[10] method. The method originally described by Rowntree and Geraghty[11] for the elimination of phenolsulphonephthalein was used. The nitrogen in the urine was determined by the method devised by Folin and Farmer,[12] and the sodium chlorid by the method suggested by Harvey.[13]

It seems most satisfactory to present the data on the individual cases in the form of tables and follow each table by a short description of the points of interest in that individual case, or by any comments that seemed appropriate. Following the presentation of the individual cases we shall give a summary of the cases taken as a whole to see what conclusions may be drawn.

The numbers used are the medical record numbers at the Peter Bent Brigham Hospital. The figures in italic in the nitrogen and salt columns signify the days on which the sodium chlorid and urea were added to the diet.

The first group of six cases (Tables 1-6, Chart 1) show types of nephritis which were unable to put out well added salt and urea. They fall into two groups: one in which the blood nitrogen varies with the diet, the other in which the blood nitrogen rises despite a low protein diet.

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10. Folin and Denis: Jour. Biol. Chem., 1912, xi, 527.
11. Rowntree and Geraghty: Jour. Pharmacol. and Exper. Therap., 1910, i, 579.
12. Folin and Farmer: Jour. Biol. Chem., 1912, xi, 493.
13. Harvey, S. C.: The Quantitative Determination of the Chlorids in the Urine, The Archives Int. Med., 1910, vi, 12.

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TABLE 1.—DATA OF PATIENT 1078

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
May										
12	1,500	985	1.016	11.0	7.6	4.0	2.8	20.0	54	128- 80
13	1,350	1,200	1.012	11.2	7.5	*14.0*	2.5	....	..	145- 98
14	1,500	730	1.016	11.2	6.5	4.0	3.6			
15	1,360	1,470	1.012	11.2	9.0	4.0	2.6	....	..	150-105
16	1,375	1,040	1.016	11.2	8.3	4.0	2.4			
17	1,635	1,440	1.013	*21.2*	10.5	4.0	2.6			
18	1,590	1,260	1.013	11.2	8.0	4.0	2.4			
19	1,610	900	1.016	11.2	7.6	4.0	2.1	....	..	130- 90
						10 KCl				
20	1,580	1,190	1.014	11.2	8.0	*14.0*	3.4			
21	1,510	1,670	1.011	11.2	8.2	4.0	4.0			
22	1,505	1,440	1.013	11.2	8.6	4.0	3.4	35.2	..	
23	1,500	1,360	1.016	23.0	12.8	4.0	2.4	....	..	120- 80
24	1,500	1,640	1.018	23.0	17.7	4.0	2.1			
25	1,500	800	1.023	23.0	12.9	4.0	0.8			
26	1,500	900	1.028	23.0	15.5	4.0	1.2	....	..	120- 80
27	1,500	960	1.024	23.0	18.6	4.0	2.2	45.0	..	
28	1,500	1,130	1.022	23.0	20.3	4.0	3.3			
29	1,500	840	1.023	17.5	14.3	4.0	1.7			
30	1,500	940	1.025	4.0	11.6	4.0	1.2	....	..	125- 85
31	1,530	900	1.014	4.0	6.2	4.0	2.6			
June										
1	1,130	400+	1.016	4.0	3.7+	4.0	0.9+			
2	1,500	1,115	1.013	4.0	6.4	4.0	2.0	....	48	130- 80
3	1,500	910	1.013	4.0	5.6	4.0	2.1	26.7	..	
4	1,390	835	1.013	14.0	6.1	4.0	1.9			
5	1,350	1,265	1.014	14.0	10.9	4.0	3.3			
6	1,520	1,565	1.011	14.0	12.1	4.0	3.3	....	..	125- 75
7	1,320	890	1.015	14.0	10.1	4.0	3.2			
8	1,305	990	1.020	4.0	4.6	4.0	2.8	31.2	..	

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TABLE 2.—DATA OF PATIENT 624

Date	Fluid Intake c.c.	Urine		Nitrogen		Chlorid		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Dec.										
17	.....	.....	.....	....	....	10.0	8.4			
18	.....	.....	.....	....	....	10.0	10.8			
19	.....	.....	.....	....	....	10.0	11.4	....	..	230-125
20	.....	1,300	.....	11.2	11.6	*14.0*	8.9			
21	1,100	1,100	.....	11.2	11.7	4.0	6.7			
22	950	900	.....	11.2	11.0	4.0	5.7	25.4	45	225-124
23	1,300	900	.....	11.2	14.2	4.0				
24	1,250	1,100	.....	11.2	12.7	4.0	....	....	..	215-120
25	1,300	850	.....	23.0	18.1	4.0				
26	1,150	1,150	.....	23.0	16.2	4.0				
27	1,410	1,200	.....	*33.0*	20.1	4.0				
28	1,350	1,450	.....	23.0	19.2	4.0				
29	1,700	1,300	.....	23.0	18.1	4.0	....	31.2	50	210-120
30	1,500	1,150	.....	23.0	Lost	4.0				
31	1,300	1,500	1.022	23.0	23.3	4.0	....	....	..	215-125
Jan.										
1	950	1,300	.....	23.0	24.0	4.0				
2	1,500	1,450	.....	11.2	11.2	4.0	....	36.5	..	220-120
3	1,300	850	1.022	11.2	13.0	4.0				
4	1,150	1,100	.....	11.2	12.5	4.0				
5	1,050	1,050	.....	11.2	11.0	4.0	....	....	..	210-140
6	1,700	1,450	1.022	11.2	10.0	4.0				
7	1,100	1,100	.....	4.0	9.0	4.0	....	28.5	50	
8	1,600	1,000	.....	4.0	7.2	4.0	....	....	..	210-130
9	1,650	750	1.010	4.0	5.5	4.0	....			
10	1,300	1,450	.....	4.0	...	...	....	21.1	54	

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Patient 1078 had cirrhosis of the liver with ascites in addition to a chronic nephritis. Salt and urea when added to the diet were excreted poorly. On both the standard and high protein diet the nitrogen excretion was less than the intake. The non-protein nitrogen of the blood rose steadily on both these diets and fell again on the low protein diet. On June 4 for four successive days 20 gm. of urea were added to the low protein diet with a slight rise in the blood nitrogen. Only two phenolsulphonephthalein observations were made during this study, and they were practically the same. The blood-pressure did not show any appreciable changes with these variations in diet. On the high protein diet the patient did not feel as well as when on the other diets and had slight nausea. Ten gm. of potassium chlorid were not excreted any more readily than the sodium chlorid.

The data in this case are recorded also in Chart 1 in order to show the points more graphically.

In Case 624 accurate observations on the amount of the diet refused by the patient were not kept. Therefore we record under "intake" the amount offered. Observation in a general way made it evident that the major part of the diet was eaten. In this study the nitrogen excretion surpassed the intake on the days of standard diet and on some of the days of high protein diet. No explanation is offered for this. In this case as in the preceding one the non-protein nitrogen of the blood rose with the high protein diet and fell with the diet poor in nitrogenous content. Also, there was no appreciable variation in the phenolsulphonephthalein output or blood-pressure during these observations. The patient had very few subjective symptoms, and no change was noted in them during the period of study.

Patient 1197 had very few subjective symptoms from the chronic nephritis except slight dyspnea on exertion and headaches. This case showed a poor ability of the kidneys to put out salt and urea when added to the diet. The blood nitrogen was high to begin with and remained elevated on the standard diet and the high protein diet, which were only fairly well eaten. On the low protein diet, however, the non-protein nitrogen of the blood very rapidly fell to normal. The blood-pressure in this case, with rest in the hospital and apparently irrespective of diet, fell steadily during this period of study. Only two phenolsulphonephthalein observations were made early in the study, and they showed no variation. The general condition of the patient

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TABLE 3.—DATA OF PATIENT 1197

Date	Fluid Intake c.c.	Urine		Nitrogen		Nitrogen		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
May										
16	1,175	240+	1.019	11.2	2.3+	4.0	1.0+	39.0	54	225-135
17	1,970	800	1.019	11.2	9.9	4.0	1.5			
18	1,185	855	1.019	11.2	9.1	*14.0*	2.0	....	..	210-130
19	1,940	1,160	1.018	11.2	13.6	4.0	3.2			
20	1,860	1,100	1.015	*21.2*	13.9	4.0	2.4	....	..	230-140
21	1,430	1,180	1.018	11.2	13.7	4.0	2.0			
22	1,730	1,020	1.016	11.2	10.2	4.0	1.1	....	..	215-130
23	1,865	1,015	1.016	11.2	9.0	4.0	0.6	43.1	50	
24	990	1,450	1.012	11.2	12.8	4.0	1.2	....	..	200-120
						KCl 10				
25	1,365	1,305	1.016	6.7	10.9	*14.0*	3.2			
26	1,465	950	1.016	11.2	10.6	4.0	1.4			
27	2,305	950	1.017	11.2	10.6	4.0	1.2	....	..	195-110
28	2,356	1,070	1.018	17.8	13.0	2.5	2.3			
29	1,940	1,220	1.015	19.8	13.5	3.0	2.5	....	..	178- 95
30	1,940	1,536	1.015	23.0	16.1	4.0	3.2			
31	1,850	1,275	1.017	22.5	13.1	4.0	4.1			
June										
1	1,800	1,320	1.014	20.5	Lost	3.5	Lost	39.6	..	180-100
2	1,760	1,600	1.011	7.0	10.6	4.0	4.5			
3	1,640	450	1.016	4.0	4.5	4.0	1.0			
4	1,640	560+	.....	4.0	Lost	4.0	Lost			
5	1,630	410+	1.010	3.6	3.0+	3.8	1.3+	25.9	..	175- 90

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TABLE 4.—DATA OF PATIENT 739

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Jan.										
16	2,100	1,500	.....	....	...	...	...	22.8	58	235- 95
17	1,300	1,150	1.017	10.7	8.8	...	...			
18	1,650	1,150	1.016	9.1	9.6	...	...	....	..	230- 85
19	900	700	1.021	10.8	7.0					
20	1,250	800	1.020	10.5	...	...	...	....	..	220- 85
21	1,000	1,290	1.012	*19.1*	9.8	...	...	41.0	32	
22	950	1,180	1.015	9.1	11.7	...	...	....	..	220- 85
23	1,100	580	1.019	7.6	7.3					
24	1,000	720	1.018	8.5	7.4					
25	900	500	1.020	10.7	5.0					
26	1,900	2,100	1.014	22.5	10.5	4.0	7.1	37.5	35	200- 90
27	1,100	900	.....	17.9	...	4.0	4.8			
28	1,300	1,100	.....	18.0	...	4.0	6.2			
29	1,950	1,300	.....	17.5	...	*14.0*	11.2	....	..	230-110
30	1,750	2,100	.....	17.5	...	4.0	9.7	36.5	52	
31	1,000	900	1.016	3.4	...	4.0	5.4	....	..	220-100
Feb.										
1	900	500	1.019	3.2	4.0					
2	1,500	900	.....	3.2	...	...	...	....	..	210- 85
3	1,300	750	.....	3.8						
4	1,400	1,300	.....	3.1	...	...	...	25.5	52	215- 80

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TABLE 5.—DATA OF PATIENT 762

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Jan.										
20	1,600	1,300	1.015	6.0	...	10.0	...	43.4	35	190-110
21	1,550	1,500	1.022	6.0	...	4.0	3.8			
22	1,500	1,580	1.018	11.2	8.0	4.0	9.2	....	..	195-125
23	2,100	1,550	1.017	11.2	9.5	4.0	9.6			
24	1,950	1,350	1.017	11.2	9.1	4.0	8.1			
25	1,500	1,300	1.016	11.2	9.3	4.0	6.8	....	..	190-120
26	1,750	1,780	1.016	*21.2*	13.2	4.0	7.5			
27	1,750	1,700	1.015	11.2	10.1	4.0	7.6			
28	1,700	1,000	1.016	11.2	7.6	4.0	4.4	50.0	..	175-110
29	2,100	1,650	1.016	11.2	11.6	4.0	7.1	....	36	
30	2,100	1,500	1.017	11.2	...	4.0	6.6			
31	1,750	1,420	1.017	11.2	...	4.0	7.5	....	..	180-110
Feb.										
1	1,950	1,500	1.015	11.2	...	4.0	5.5			
2	1,900	1,500	1.015	23.0	...	*14.0*	6.5			
3	1,950	1,550	1.017	23.0	...	4.0	5.0	47.6	26	190-120
4	2,250	2,800	1.014	23.0	...	4.0	10.2			
5	2,300	2,050	1.019	21.5	...	4.0	6.5			
6	2,100	1,900	1.017	23.0	...	4.0	5.2	56.1	..	195-130
7	2,300	1,700	1.018	4.0	...	4.0	2.4	....	18	
8	2,100	1,900	1.014	4.0	...	4.0	5.8			
9	2,100	1,900	1.016	4.0	...	4.0	5.6	....	..	180-125
10	2,300	1,300	.....	4.0	...	4.0				
11	1,900	1,650	.....	4.0	...	4.0	...	44.7		
12	1,500	1,600	1.012	4.0	...	4.0	....	....	16	180-130
13	1,500	1,150	.....	4.0	...	4.0				
14	1,590	1,100	1.015	4.0	...	4.0				
15	1,500	1,100	.....	4.0	...	4.0	...	39.8	18	

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16	1,500	790	.....	11.2	...	4.0				
17	1,500	1,220	.....	11.2	...	4.0	...	....	..	175-125
18	750	700	.....	4.0	...	2.0				
19	1,500	1,100	.....	11.2	...	4.0				
20	1,500	1,700	.....	11.2	...	4.0				
21	1,500	1,170	1.017	11.2	...	4.0	...	78.6	15	170-120
22	1,600	1,120	.....	11.2	...	4.0				
23	1,500	1,490	.....	11.2	...	4.0				
24	1,500	1,700	.....	11.2	...	4.0	...	....	..	150-115
Mar. 7	*							86.0	33	

* From Feb. 24 to March 7, diet 11.2 gm. nitrogen, 4 gm. salt each day.

TABLE 6.—DATA OF PATIENT 1056

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
April										
12	1,500	1,200	1.014	1.3	4.1	2.0	4.0	78.9	Trace	
13	1,500	720	1.013	1.5	3.8	2.0	2.5	....	..	210-105
14	1,900	680	1.015	1.5	5.7	2.0	2.1			
15	1,850	820	1.015	0.6	2.2	*12.0*	2.9	....	..	210-105
16	1,750	230	1.013	0.0	0.7	0.0+	0.7			
17	1,750	410	1.015	0.0	2.1	0.0+	1.6	86.9	Trace	
18	1,700	860	1.014	0.0	3.7	0.0+	2.9	....	..	200-100
19	1,100	435	1.012	*10.0*	1.8	0.0+	1.7			
20	1,700	1,230	1.014	1.8	6.4	2.0	3.6	....	..	180- 90
21	2,000	800	1.020	2.4	5.2	3.4	7.4			
22	1,500	675	1.016	2.5	4.1	3.0	1.7	129.9	Trace	
23	?	630	1.015	4.0	2.8	4.0	1.7	....	..	210-100

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varied very little with the change of diets, but showed a gradual improvement throughout her stay in the hospital.

Case 739, of chronic nephritis with slight subjective symptoms of hypertension, showed fair ability to put out added salt, but very little

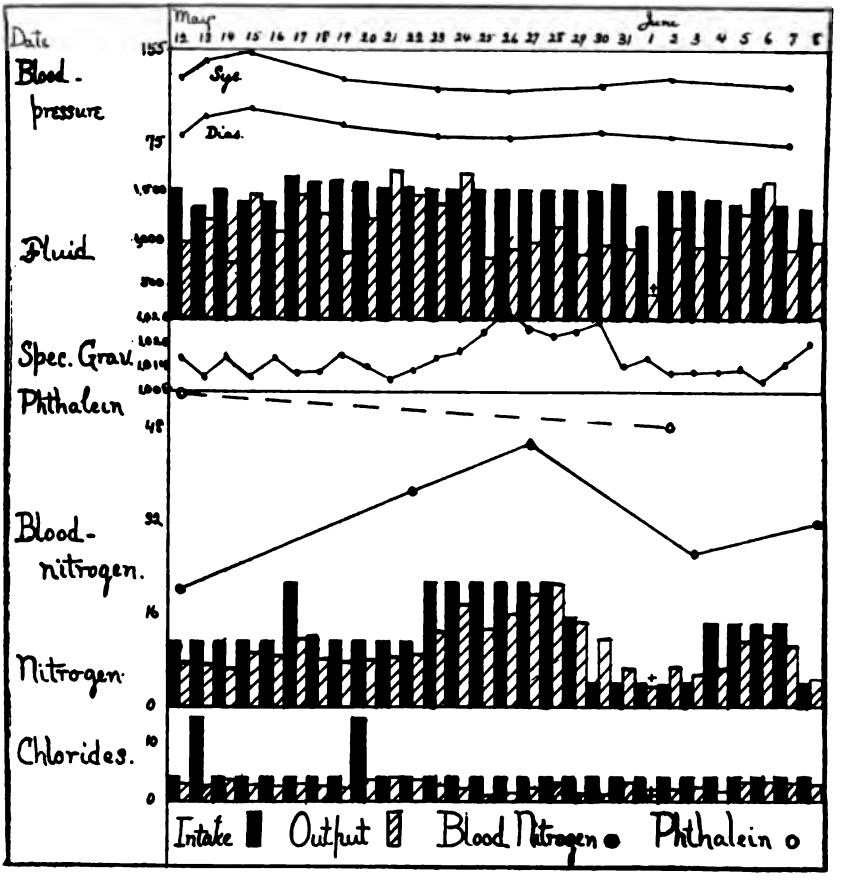

Chart 1.—Data of Patient 1078.

ability to put out added urea. Although the urinary nitrogen was fairly well excreted on the standard diet there was a sharp rise in the non-protein nitrogen of the blood on this diet. This was maintained but not elevated by the high protein diet, which was only fairly well eaten.

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On the low protein diet the blood nitrogen as in the other cases returned to normal. In this case the phenolsulphonephthalein excretion fell as the blood nitrogen rose, but returned to normal before the blood nitrogen reached normal again. The blood-pressure and general condition in this case showed practically no variations with the changes in diet.

Case 762, of nephritis, entered with a moderate amount of edema and slightly broken cardiac compensation. The ability to put out added salt and urea was poor. The nephritis as shown by the non-protein nitrogen of the blood and by the phenolsulphonephthalein test was of a moderately severe grade. The diets were eaten extremely well. On a standard and high protein diet the non-protein nitrogen of the blood rose and the phenolsulphonephthalein elimination fell. The patient did not seem in as good general condition at this time. On a low protein diet the blood nitrogen fell, but the phenolsulphonephthalein excretion remained the same. Then on a standard diet the blood nitrogen suddenly began to rise quite markedly, and eventually the phenolsulphonephthalein excretion rose. At the same time the blood-pressure fell, and the general condition of the patient became so improved that he went home. The edema disappeared as the stored-up salt was gradually eliminated. Two months later the patient reported to the outpatient department in pretty fair shape with a non-protein blood nitrogen of 46 mg. per hundred c.c. of blood. This unexpected rise on the standard diet to a higher level than formerly we cannot explain.

Case 1056 represented a severe nephritis with symptoms suggestive of pending uremia without edema. The patient did not change in condition while in the hospital and left against advice. For several days practically no diet was eaten. Added salt or urea were very poorly excreted. The phenolsulphonephthalein excretion remained only a trace throughout. The non-protein nitrogen content of the blood rose steadily even on a very low protein diet. The blood-pressure made no important fluctuations.

The next group of five cases (Tables 7-11, Chart 2) show types of nephritis which apparently can eliminate added nitrogen in the form of urea or the nitrogen of a standard diet fairly well, but which cannot put out added salt well. The non-protein nitrogen of the blood, however, becomes elevated on the high protein diet. As in the other group it returns to normal on the low protein diet.

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TABLE 7.—DATA OF PATIENT 1097

Date	Fluid Intake c.c.	Urine		Nitrogen		Chlorid		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
April										
20	.....	.....	.....	....	...	...	...	43.4	40	190-110
21	1,300	340	1.021	4.0	5.0	1.0	0.2	....	..	215-115
22	1,000	1,865	1.016	4.0	13.2	1.0	9.0			
23	800	5,800	1.013	4.0	7.9	1.0	38.0	....	..	215-120
24	800	1,200	1.018	4.0	4.8	6.0	8.6			
25	1,000	1,400	1.016	6.0	7.1	6.0	4.0	....	..	230-130
26	1,000	310	1.022	6.0	5.3	6.0	1.6			
27	1,000	837	1.020	6.0	8.0	6.0	2.3			
28	1,300	990	1.020	6.0	7.4	6.0	2.8	....	..	210-120
29	1,200	885	1.018	6.0	6.1	6.0	3.0			
30	1,200	1,030	1.019	6.1	8.5	6.0	4.0			
May										
1	1,500	890	1.022	6.0	7.7	*16.0*	4.5			
2	1,250	550+	1.018	6.0	3.5+	6.0	7.7+	....	..	195-110
3	1,500	700	1.019	6.0	4.7	6.0	5.5			
4	1,200	1,465	1.017	*16.0*	12.5	6.0	9.6	....	..	180-100
5	1,500	410+	1.020	6.0	2.6+	6.0	3.2+	....	51	
6	1,300	Lost	Lost	6.0	Lost	6.0	Lost			
7	1,300	840	1.018	11.2	6.4	4.0	5.2			
8	1,500	1,465	1.017	11.2	13.1	*14.0*	10.2	32.2	..	190- 85
9	1,500	980	1.020	11.2	7.0	4.0	5.8			
10	1,200	1,165	1.022	11.2	13.4	4.0	5.2			
11	1,550	950	1.022	11.2	10.7	4.0	5.0	....	51	200-100
12	1,250	1,310	1.013	11.2	8.0	4.0	3.7			
13	1,075	1,015	1.015	10.7	9.1	4.0	1.0			
14	1,100	600+	1.020	23.0	8.1	4.0	0.6+			
15	1,250	1,570	1.018	23.0	19.3	4.0	3.0	....	..	180- 90
16	1,300	920	1.021	22.5	10.6	4.0	2.2			
17	1,680	960	1.020	23.0	12.3	4.0	2.0			
18	1,550	960	1.021	23.0	9.4	KCl 10 *14.0*	5.7	46.3	..	
19	1,250	910	1.020	8.4	11.8	4.0	4.4	....	40	
20	1,640	650	1.020	4.0	8.9	4.0	3.4			
21	1,730	1,058	1.010	4.0	5.3	4.0	3.0			
22	1,810	980	1.012	4.0	4.6	4.0	4.0			

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TABLE 8.—DATA OF PATIENT 428

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Nov.										
7	1,000	1,130	.....	8.0	7.0	6.0	10.3			
8	1,000	1,265	.....	8.0	8.0	6.0	11.5			
9	1,000	1,665	.....	8.0	6.3	*16.0*	12.3			
10	1,000	1,465	.....	8.0	6.0	6.0	10.8			
11	1,000	2,050	.....	*18.0*	14.0	6.0	16.8			
12	1,000	1,316	.....	8.0	...	6.0	10.0			
28	1,000	1,300	1.020	11.2	...	4.0	...	21.5	51	
29	1,000	900	.....	11.2	...	4.0	...	....	..	122- 80
30	1,000	900	.....	11.2	...	4.0	...			
Dec.										
1	1,000	1,050	1.020	11.2	...	4.0	...	....	..	140- 94
2	1,000	980	.....	11.2	9.7	4.0				
3	1,000	840	.....	11.2	14.2	4.0				
4	1,000	1,450	.....	11.2	15.0	4.0	...	20.2	..	136- 90
5	1,000	1,360	.....	23.0	20.6	4.0				
6	1,000	1,050	.....	23.0	19.6	4.0				
7	1,800	1,650	.....	23.0	19.0	4.0				
8	1,800	1,540	.....	23.0	17.0	4.0	...	39.1	45	140- 90
9	1,800	1,600	.....	11.2	13.0	4.0				
10	1,800	1,200	.....	11.2	14.0	4.0				
11	1,800	1,300	.....	11.2	13.4	4.0	...	....	..	140- 94
12	1,800	1,150	.....	11.2	9.9	4.0	...	28.5		
13	1,800	1,180	1.030	11.2	10.6	4.0				
14	1,800	1,090	.....	11.2	11.8	4.0				
15	1,800	1,030	1.012	11.2	9.4	4.0				
16	1,800	950	.....	11.2	7.5	4.0		....	..	142- 84
17	1,800	980	1.020	11.2	6.7	4.0	...	23.9	45	
18	1,800	1,020	.....	4.0	7.6	4.0				
19	1,800	780	1.021	4.0	...	4.0	...	....	..	142- 92
20	.....	.....	.....	4.0	...	4.0				
21	.....	.....	.....	4.0	...	4.0	...	19.6	..	

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Patient 1097 entered the hospital in poor condition and showed auricular fibrillation and extensive edema. The edema quickly disappeared with the tremendous diuresis April 23. The non-protein nitrogen in the blood was above normal on admission. Added salt to the diet on May 1 was put out very poorly by the kidneys. Added urea was put out fairly well. The output of nitrogen in the urine the first few days was in excess of the intake, which suggested a high protein intake or retention with the edema before admission. This was consistent with the high non-protein nitrogen in the blood at entrance. On the standard and low protein diet the nitrogen was excreted well and the blood nitrogen dropped to nearly normal. On the high protein diet which this patient ate well the output of nitrogen in the urine did not approximate the intake so closely. During this period of high protein diet following the standard diet the non-protein nitrogen of the blood again rose. It took apparently a larger amount of nitrogen intake to cause an increase in blood nitrogen. Again, on May 20, when the low protein diet was given, the urinary nitrogen exceeded the intake and the non-protein nitrogen of the blood fell. During the entire period of study the phenolsulphonephthalein excretion ranged from 40 to 51 per cent. It was higher when the blood nitrogen was lower. Ten gm. of potassium chlorid added to the diet were not excreted any better than sodium chlorid.

The blood-pressure showed some variations during the stay in the hospital, but not in any special relation to the diets. It tended to be lower the longer the patient was in the hospital, despite the period of high protein diet. On leaving the hospital the patient had no edema, his general condition was improved and the auricular fibrillation persisted.

In patient 428 the amount of food actually eaten was not measured, so the amount offered is recorded. Frequent observations, however, made us feel pretty certain that practically everything offered was consumed. This patient showed early in November an ability to put out urea when added to the diet, but not salt. As in the preceding case it was necessary to put the patient on the high protein diet in order to elevate the non-protein nitrogen in the blood. On the low protein or standard diets the nitrogen in the blood remained normal. The phenolsulphonephthalein excretion and the blood-pressure showed no appreciable variation with the changes in diet. By the time this study was

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TABLE 9.—DATA OF PATIENT 1154

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
May										
8	2,500	2,254	1.010	11.2	13.0	4.0	10.7	30.9	45	
9	1,950	1,305	1.013	11.2	9.1	4.0	5.8	....	..	220-140
10	1,350	1,020	1.021	11.2	10.3	4.0	5.3			
11	1,500	765	1.025	11.2	6.5	*14.0*	2.4			
12	1,450	940	1.026	9.9	10.9	4.0	3.6	....	..	260-160
13	1,800	600	1.016	11.2	7.1	4.0	1.1	....	..	255-155
14	2,700	3,300	1.010	*20.7*	19.1	4.0	4.3	....	60	230-150
15	2,100	940	1.020	9.9	9.3	4.0	1.4			
16	1,900	1,830	1.017	9.7	9.3	4.0	0.9			
						KCl 10				
17	2,100	1,150	1.011	8.7	7.3	*14.0*	2.7			
18	1,700	1,330	1.013	20.0	8.8	2.0	4.9	....	..	220-150
19	1,650	1,245	1.013	22.5	12.0	4.0	2.8	35.1	..	
20	1,650	1,810	1.014	20.0	13.7	2.0	4.1	....	..	210-140
21	1,750	1,070	1.015	11.2	8.0	2.0	1.5			
22	1,670	965	1.015	8.4	7.8	2.0	1.0			
23	3,100	2,980	1.005	4.0	7.0	4.0	2.0	37.3	51	205-130
24	2,130	930	1.010	4.0	5.3	4.0	1.3			
25	1,910	1,165	1.010	4.0	5.9	4.0	3.0			
26	950	740	1.011	4.0	3.7	4.0	1.2	....	..	180-110
27	1,730	365	1.018	4.0	3.8	4.0	1.2	33.1		
28	1,500	650	.....	4.0	...	4.0				
29	1,700	1,100	.....	6.3	...	2.0				
30	1,300	850	.....	11.2	...	4.0	...	....	..	190-120
31	1,900	1,150	1.012	10.7	5.7	4.0	3.0	32.6		
June										
1	1,960	1,440	1.010	10.7	6.0	4.0	2.6	....	..	170-110
2	1,750	1,460	1.010	17.8	9.0	3.5	3.0			
3	1,800	1,150	1.014	18.6	9.2	3.6	2.6			
4	1,525	1,430	1.011	19.6	9.6	4.0	2.0			
5	1,825	1,530	1.012	20.5	9.2	3.5	4.6	41.3	..	150-100

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TABLE 10.—DATA OF PATIENT 1075

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
April										
15	800	980	1.025	4.0	14.1	1.0	3.1	....	..	190-110
16	800	800	1.025	4.0	7.2	1.0	3.2	23.8	55	175- 95
17	800	645	1.026	4.0	10.0	1.0	3.0			
18	1,000	910	1.022	8.0+	8.6	3.0+	7.2			
19	1,000	1,100	1.020	8.0+	9.9	3.0+	10.5			
20	1,000	875	1.021	8.0+	7.5	3.0+	7.8	....	..	165- 90
21	1,550	1,280	1.016	11.2	7.0	4.0	8.8			
22	1,600	1,560	1.018	11.2	9.7	4.0	7.6			
23	1,600	2,340	1.014	11.2	10.5	4.0	10.2	....	..	165-100
24	1,700	2,740	1.012	*21.2*	17.8	4.0	13.0			
25	1,650	2,125	1.015	11.2	12.8	4.0	7.6			
26	1,550	1,300	1.019	11.2	7.2	4.0	8.4	20.7		
27	1,400	1,590	1.017	11.2	8.2	4.0	6.8	....	62	155-100
28	1,500	1,940	1.013	11.2	8.1	4.0	4.2			
29	1,300	1,350	1.018	23.0	18.9	4.0	3.5			
30	1,400	1,450	1.026	23.0	17.8	4.0	4.8	....	..	160- 95
May										
1	1,200	820	1.023	23.0	7.8	*14.0*	3.7			
2	1,700	1,340	1.025	23.0	15.8	4.0	7.7	....	..	140- 95
3	1,700	1,310	1.023	23.0	15.3	4.0	3.6			
4	1,700	940	1.021	23.0	12.4	4.0	2.0			
5	1,900	780	1.019	23.0	9.6	4.0	2.2	....	..	140- 95
6	1,700	1,665	1.018	23.0	20.0	4.0	2.0	36.5	45	

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TABLE 11.—DATA OF PATIENT 817

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Feb.								....	..	210-140
2	.....	.....	.....	11.2	...	4.0	...	....	56	
3	2,000	1,300	1.022	11.2	...	4.0	...	31.8	..	220-145
4	2,100	700	.....	11.2	...	4.0	...			
5	1,700	850	.....	11.2	...	4.0		....	..	200-130
6	1,950	750	1.023	11.2	11.6	4.0	2.4			
7	1,900	750	1.027	11.2	12.3	4.0	1.4	30.0	53	
8	1,950	850	1.023	11.2	12.0	4.0	1.0	....	..	200-135
9	2,100	1,100	1.022	*20.2*	18.1	4.0	1.4			
10	1,950	950	1.027	11.2	15.2	4.0	1.8			
11	1,600	950	1.027	11.2	...	*14.0*	4.0	....	..	195-130
12	1,500	750	1.027	23.0	...	4.0	3.6			
13	2,000	750	1.028	23.0	...	4.0	1.2			
14	1,500	950	1.026	23.0	...	4.0	3.2	....	..	195-130
15	1,500	950	1.025	21.5	...	4.0	3.2	35.2	51	
16	1,500	1,150	1.025	18.5	...	4.0	5.4			

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made the patient was practically without symptoms except slight edema and remained so during the study.

Patient 1154 is again an example of a marked retention of added salt. In putting out his added urea it is interesting to note that it caused a diuresis as is frequently seen. He was also unable to excrete potassium chlorid any better than sodium chlorid. It was only on a high protein diet, which he ate fairly well, that the non-protein nitrogen of the blood rose, although throughout the study the blood nitrogen was on the upper border of normal limits. The phenolsulphonephthalein elimination varied a little, but not with any special change in diet. The blood-pressure showed a steady tendency to fall during the period of study, which was from the beginning of his stay in the hospital, but did not seem to bear any relation to the diets. The general condition showed slight improvement with his stay in the hospital irrespective of diet, although the albuminuric retinitis and anemia from which he suffered changed but little.

The data in this case also are recorded in Chart 2 in order to bring out the essential points more clearly.

Patient 1075 had marked edema and poor ability to excrete salt. As the salt was eliminated the edema disappeared and the blood-pressure fell steadily irrespective of the nitrogen content of the diet. The nitrogen elimination was good on the low protein and standard diets, and it was only after prolonged high protein diet, which was well taken, that the non-protein nitrogen of the blood rose. The phenolsulphonephthalein elimination fell slightly with the rise in blood nitrogen.

Case 817 is included as it shows changes similar to those in the preceding case, except that there was no edema.

The next four cases (Tables 12-15) were controls in persons, so far as we could tell, absolutely free from nephritis. Three of them were placed on a high protein diet following the standard diet, and one on a low protein after the standard diet. The diets were well taken and accurately measured. It will be readily seen that the high protein diet was taken for a considerable time without rise in the non-protein nitrogen of the blood; nor was there any appreciable drop in the patient's non-protein nitrogen of the blood after the low protein diet.

The next two cases (Tables 16 and 17) did not have the added salt and urea tests made, but seem worth recording because of the sharp

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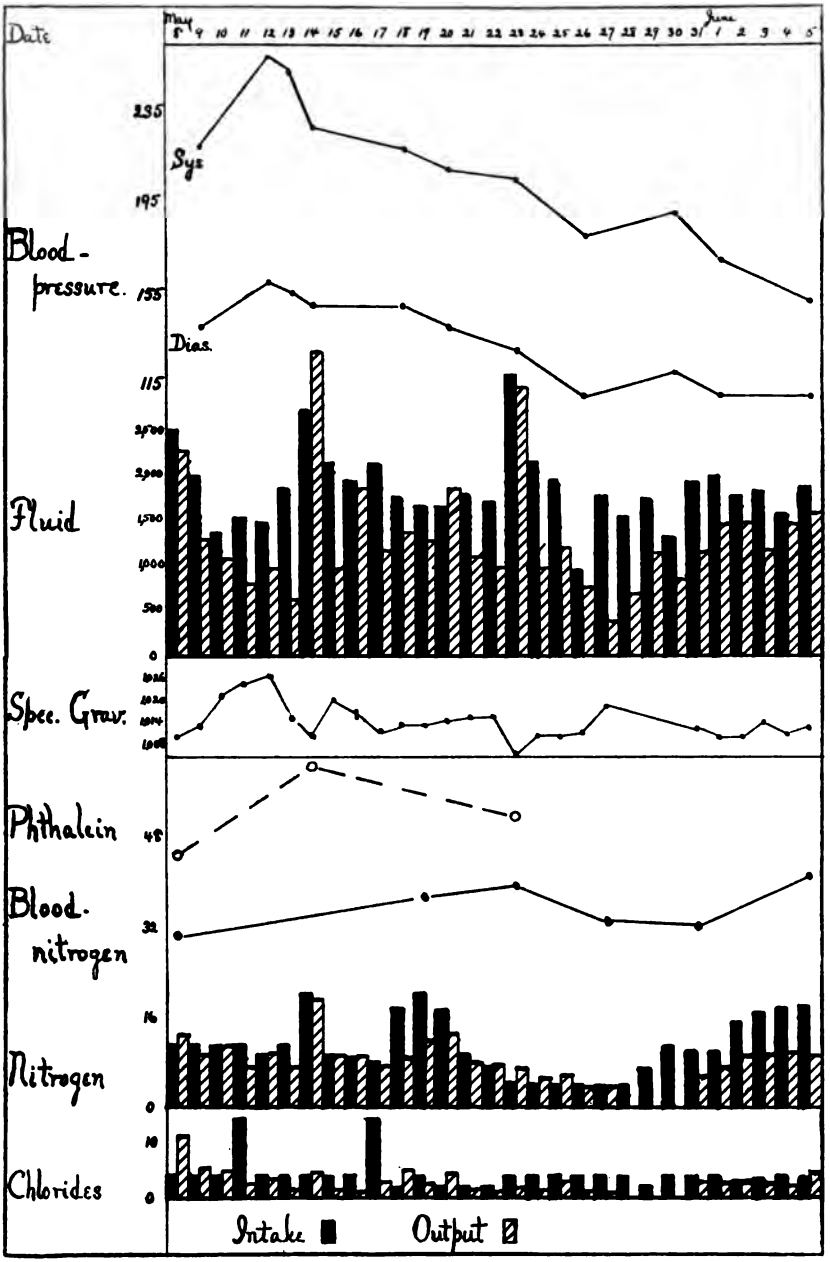

Chart 2.—Data of Patient 1154.

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TABLE 12.—DATA IN CASE 1200 (CONTROL)

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
May										
30	1,650	1,820	1.015	11.2	11.4	*14.0*	11.0	23.8		
31	1,460	1,700	1.016	*21.2*	20.2	4.0	5.6			
June										
1	1,350	990	1.020	11.2	13.6	4.0	2.0			
2	1,375	925	1.024	23.0	16.0	4.0	2.0	25.3		
3	950	1,020	1.020	17.8	16.0	3.0	4.0			
4	1,425	1,230	1.018	22.0	15.4	3.8	2.7			
5	1,475	2,290	1.015	22.0	18.2	3.8	11.4			
6	1,725	1,180+	1.014	23.0	10.6+	4.0	3.6+	22.4	58	
7	1,425	760	1.025	22.0	15.2	3.8	2.0			
8	1,280	1,660	1.015	10.0	...	4.0	2.2			

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TABLE 13.—DATA IN CASE 1033 (CONTROL)

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
April										
11	1,500	1,100	.....	11.2	....	4.0				
12	1,600	900	.....	11.2	....	4.0				
13	1,500	1,400	.....	11.2	....	4.0				
14	1,250	550	1.026	11.2	....	4.0				
15	1,300	1,150	.....	11.2	....	4.0				
16	1,500	1,150	.....	11.2	....	4.0	...	21.6	58	
17	1,650	580	.....	11.2	....	4.0				
18	1,350	1,300	.....	11.2	....	4.0				
19	1,100	900	.....	11.2	....	4.0				
20	1,650	900	.....	11.2	....	4.0				
21	1,850	500	1.018	11.2	....	4.0				
22	1,610	900	.....	11.2	....	4.0	...	17.6		
23	2,100	1,100	.....	23.0	....	4.0				
24	2,100	1,100	.....	23.0	....	4.0				
25	1,950	700	.....	23.0	....	4.0				
26	1,900	700	.....	23.0	....	4.0				
27	1,800	580	.....	23.0	....	4.0				
28	1,850	500	.....	23.0	....	4.0	...	20.6		

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TABLE 14.—DATA IN CASE 920 (CONTROL)

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Mar.										
26	1,500	2,300	.....	10.5	....	3.8	...	....	..	125 -50
27	1,500	1,800	1.022	11.2	....	4.0	...	27.0	..	115- 50
28	1,500	1,700	.....	11.2	....	4.0	...	....	58	
29	1,500	1,450	.....	10.7	....	4.0				
30	1,500	950	.....	11.2	....	4.0				
31	1,500	1,350	.....	21.5	....	3.8				
April										
1	1,500	1,300	.....	23.0	....	4.0	...	....	..	140- 80
2	1,500	1,150	.....	22.9	....	4.0				
3	1,500	1,750	.....	23.0	....	4.0				
4	1,500	1,580	.....	21.5	....	3.8	...	26.6	..	150- 80

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TABLE 15.—DATA IN CASE 1252 (CONTROL)

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
June										
18	1,400	1,100	.....	11.2	....	4.0				
19	2,300	1,900	.....	11.2	....	4.0	...	20.1	..	150- 90
20	1,500	2,150	1.008	4.0	....	4.0				
21	2,260	1,660	1.008	4.0	4.0	4.0	3.2			
22	1,450	1,160	1.009	4.0	4.2	4.0	2.3			
23	2,100	200+	.....	4.0	....	4.0	...	19.2		

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TABLE 16.—DATA OF PATIENT 589

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Dec.										
5	1,100	1,500	1.009	6.0	....	6.0	...	20.8	27	
6	1,200	1,350	.....	6.0	....	6.0	...	....	..	198-115
7	1,200	1,040	.....	6.0	....	6.0				
8	1,420	2,100	.....	11.2	....	4.0				
9	1,360	1,300	1.014	11.2	....	4.0	...	....	..	195-110
10	1,200	1,700	1.015	11.2	....	4.0	...	....	50	
11	1,200	1,500	1.018	11.2	4.2	4.0				
12	950	1,050	.....	11.2	5.3	4.0				
13	950	1,100	1.018	23.0	5.8	4.0	...	....	..	170-100
14	1,200	900	.....	23.0	8.5	4.0				
15	1,300	1,550	.....	23.0	12.1	4.0	...	43.5	24	

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TABLE 17.—DATA OF PATIENT 785

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
June										
5	3,145	1,840	1.009	9.2	5.1	4.0	5.1	....	0	
6	2,750	1,300	1.009	10.0	3.0	4.0	3.0	117.0	0	130- 90
7	1,305	1,220	1.007	9.8	4.0	4.0	2.8			
8	2,595	460	1.007	7.0	1.5	3.5	0.64	130.0	0	135- 95
9	1,000	450	1.011	9.2	1.3	3.5	0.72	....	..	†
10	2,700	380	.....	4.6	....	2.0	...	179.0	0	180- 80
11	2,500	150	.....	4.0	2.0					
12	1,300	0	.....	0.0	....	0.0	...	....	..	140- 65
13	Died									

† Convulsion.

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TABLE 18.—DATA OF PATIENT 1072

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
April										
16	1,100	1,480	1.015	10.7	3.1	4.0	7.2	....	..	190-100
17	1,300	1,100	1.010	9.7	3.0	3.0	1.2	31.8	60	
18	950	840	1.015	10.7	6.3	*14.0*	4.0	....	..	200-110
19	1,300	1,180	1.009	8.8	3.5	3.0	2.7			
20	1,300	2,400	1.010	*18.7*	8.2	4.0	6.7	....	..	210-112
21	1,500	1,810	1.010	10.7	8.0	4.0	3.2			
22	1,680	1,915	1.010	11.1	7.4	4.0	4.0	....	..	185- 95
23	1,900	1,190	1.011	10.0	4.1	4.0	4.6			
24	1,300	2,060	1.011	12.6	3.7	4.0	2.8	29.4	..	180-100
25	1,500	1,150	1.015	17.3	7.1	3.0	1.0			
26	1,300	1,630	1.012	17.3	8.2	3.0	1.9			
27	1,500	1,320	1.011	19.0	7.5	3.0	1.2			
28	1,550	2,045	1.011	20.4	7.0	3.5	2.4	....	..	185-100
29	1,400	1,565	1.012	17.0	6.0	3.0	2.0			
30	1,500	1,570	1.013	17.0	8.4	3.0	2.5	....	..	180-100
May										
1	1,350	1,630	1.012	19.7	8.1	3.0	2.0	34.0		
2	1,500	1,450	1.010	13.0	6.7	2.0	1.6	....	..	178-100
3	1,350	1,460	1.008	4.0	4.8	4.0	1.5			
4	1,200	1,092	1.010	4.0	4.6	4.0	1.9	....	..	170- 98
						KCl 5				
5	1,100	1,355	1.010	4.0	2.8	*9.0*	7.2	23.7	51	

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rise in non-protein nitrogen of the blood, in Case 589, on a high protein diet, and in Case 785, on a diet very low in nitrogen. The latter patient died the day following the last estimation of blood nitrogen.

It would not be fair to omit the following four cases (Tables 18-21) which show varying degrees of inability to put out added salt and urea. They also show other evidences of nephritis, yet very little if any rise in non-protein nitrogen in the blood on even high protein diet. In these cases, also, there seems to be no relation between the phenolsulphonephthalein excretion or the blood-pressure and the diets. The general condition of the patients did not vary with the diets. Their symptoms were slight in all the cases. In all these cases the non-protein nitrogen of the blood fell to the lower level of normal limits on the low protein diet.

In endeavoring to draw any conclusions from such a study as this or from any study of nephritis, it must be borne in mind that it is frequently impossible to decide accurately what type of nephritis from a pathological-anatomical point of view we are dealing with. In this study in most of the cases the kidneys have been studied from the point of view of their functional ability rather than with any attempt to classify the cases on an anatomical basis. The functional tests consisting in the addition of salt and urea to the diet do not permit in our series of cases such a sharp classification as Widal makes. Apparently, cases do occur in which the salt is not excreted and the nitrogen is. In the cases with a nitrogen retention, however, of our series the salt was also poorly excreted.

It is safe to say that not all of our cases of presumably the same type of functional renal disturbance act in the same way in response to the changes in diet. On the other hand, the majority of them do. Thus those cases which eliminate added urea and salt poorly tend to show an increase in the non-protein nitrogen of the blood on a diet not excessive in nitrogen, while those cases which excrete urea well but salt rather poorly, only show an increase in non-protein nitrogen of the blood on a diet rich in protein.

We find, as did Folin, Denis and Seymour, that the elimination of phenolsulphonephthalein in the urine in most of these cases of nephritis does not vary especially with the diets. In a few cases, however, it follows in a slight degree inversely to the changes in the non-protein nitrogen of the blood.

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TABLE 19.—DATA OF PATIENT 675

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Jan.										
7	1,750	1,100	1.012	4.0	....	4.0				
8	1,780	1,150	.....	4.0	....	4.0	1.9			
9	1,170	300+	.....	4.0	....	4.0	3.5	34.0	54	170-105
10	1,200	700	.....	4.0	....	4.0	2.3			
11	1,160	500	.....	4.0	....	*14.0*	6.5			
12	1,100	900	.....	4.0	4.1	4.0	5.2	....	..	145- 85
13	1,100	900	.....	4.0	4.7	4.0	4.0			
14	1,650	900	.....	8.4	4.8	3.6	...	21.6	55	
15	1,550	1,300	1.022	*21.2*	12.3	4.0	...	....	..	150- 90
16	1,550	1,300	1.016	11.2	9.2	4.0				
17	1,500	750	1.021	11.2	8.7	4.0				
18	1,520	880	1.011	7.9	7.4	3.0	...	26.3	..	145- 90
19	1,150	500	.....	6.9	....	3.0	...	....	51	
20	800	580	.....	6.8	....	3.0	...	....	..	140- 85
21	550	1.080	.....	19.8	....	3.0				
22	1,700	1,260	1.015	13.0	8.2	2.0				
23	1,100	1,020	1.012	13.0	7.0	2.0	...	....	..	145- 85
24	1,550	820	1.015	13.0	6.0	2.0				
25	950	1.250	.....	11.2	....	2.0	...	29.0	43	150- 90

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TABLE 20.—DATA OF PATIENT 1029

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
April										
12	900	570	1.021	11.0	3.1	4.0	2.8			
13	1,300	1.080	1.014	5.2	5.0	2.0	3.8	28.5	60	220- 95
14	1,300	430	1.020	6.7	4.0	2.0	0.86			
15	1,500	520	1.026	2.7	6.0	*12.0*	3.7	....	..	185- 90
16	1,300	305	1.021	4.0	1.8	2.0	2.4			
17	1,100	300	1.028	5.1	3.8	2.0	1.2	....	..	190- 90
18	1,300	510	1.013	*15.1*	6.2	2.0	0.9			
19	1,300	605	1.015	6.7	5.5	2.0	1.3			
20	1,100	305	1.026	6.7	5.1	2.0	0.9	....	..	185- 95
21	1,300	830	1.015	15.7	5.6	2.6	1.7	19.5	75	180- 95
22	1,300	1,010	1.013	9.7	6.0	1.8	3.0			
23	1,500	440	1.026	10.7	5.5	2.0	2.8			
24	1,300	1,115	1.020	20.0	9.0	3.8	4.2			
25	1,300	500	1.026	12.0	7.0	2.1	1.1	....	..	185- 80
26	1,300	760	1.020	14.3	8.7	2.5	2.2			
27	1,650	1,800	1.017	14.4	11.1	2.5	2.3			
28	1,600	1,270	1.020	14.0	10.8	2.5	1.1			
29	1,650	1,530	1.016	15.0	9.8	2.6	3.4	21.7		
30	1,300	1,132	1.022	15.0	11.3	2.6	2.0	....	..	205-105

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TABLE 21.—DATA OF PATIENT 684

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Jan.										
6	950	480	.....	11.2	....	4.0	...	35.9	65	210-100
7	700	690	.....	11.2	....	4.0				
8	1,150	300	.....	11.2	....	4.0				
9	1,250	700	.....	4.0	....	4.0	5.2	....	..	200-110
10	1,900	1,300	.....	4.0	....	4.0	3.0			
11	1,380	1,700	.....	4.0	....	4.0	3.0			
12	2,100	1,780	.....	4.0	3.2	*14.0*	6.2	....	..	220-130
13	1,150	910	.....	4.0	4.2	4.0	7.1			
14	1,900	2,100	.....	11.2	8.4	4.0	4.5	23.3	70	
15	1,900	1,700	1.015	*21.1*	16.0	4.0	...	....	..	210-110
16	1,380	1,950	1.014	11,2	12.6	4.0	...			
17	1,700	1,500	1.012	11.2	6.3	4.0	...	....	..	200-110
18	1,700	1,500	1.011	10.7	....	4.0				
19	1,650	1,900	.....	10.8	....	4.0	...	27.7	57	
20	2,000	1,590	.....	10.7	....	4.0	...	....	..	200-110
21	1,350	1,280	1.012	10.7	8.1	4.0				
22	1,300	1,100	1.019	8.2	10.8	1.5	...	....	..	180-108
23	1,650	980	1.026	21.0	17.0	3.6				
24	2,650	1,750	1.015	21.0	15.0	3.6				
25	1,650	1,620	.....	21.5	....	3.8				
26	2,100	2,300	.....	....	...	...	...	21.0	47	220-120

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The blood-pressure did not seem to vary with the amount of nitrogen in the diet or of non-protein nitrogen in the blood as Goodall described it. It did seem to fall gradually after rest in the hospital, and especially in those cases of salt retention after the salt had been eliminated by a prolonged diet low in sodium chlorid content.

The general condition of the patient did not seem to be affected by the diets except in a few cases on the high protein diet, at which time the patients did not feel so well. This is somewhat different from Seymour's findings in which the high protein diet usually made the patients feel poorly. In his cases, however, the high protein diet was continued a longer time. The high protein diet as a rule was not enjoyed by many of the patients.

The low protein diet almost always caused a drop in the non-protein nitrogen of the blood.

Since frequently the variation in the amount of non-protein nitrogen in the blood is the only result of the changes in diet which can be made out, the question may fairly be raised of how much value in prognosis is a rise in the non-protein nitrogen in the blood when brought about by an increased nitrogen content in the diet. Is there any appreciable change in the patient's renal condition with these changes in diet which only this test will show? These questions cannot be answered at present, but undoubtedly the diet should be considered when the amount of non-protein nitrogen in the blood is used as a basis for determining the prognosis. Presumably a rise in non-protein nitrogen in the blood in response to increased protein in the diet indicates a slighter degree of renal disturbance than is indicated by a rise when the patient is on a low protein diet.

It seems justifiable to conclude that in certain types of chronic nephritis the nitrogenous content of the diet should be carefully watched in order to prevent an increase in non-protein nitrogen in the blood. The exact effect of an increase in blood nitrogen produced by a high nitrogenous diet is not known at present, but presumably it is unfavorable to the best interests of the patient, since in some it increases their discomfort as shown by Cases 1078 and 762 of this series and cases studied by Seymour. A diet low in nitrogen content will frequently keep down to normal the non-protein nitrogen of the blood in chronic nephritis.

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ABSTRACT OF DISCUSSION

Dr. L. G. Rowntree, Baltimore: What were the results of Dr. Frothingham's examination of phenolsulphonephthalein excretion on a high and low protein diet in Case 2 and Case 3, and on what evidence does he base his conclusions with regard to the greater variations in the phenolsulphonephthalein excretion as compared with the total non-protein nitrogen in cases of nephritis? According to Dr. Frothingham's statement, the nitrogen of the blood varies with the diet. The phthalein excretion is not affected by diet — so far as our studies are concerned.

Dr. DeLancey, Rochester, N. Y.: Does Dr. Frothingham make any distinction in the protein from meat, eggs or milk?

Dr. Louis F. Bishop, New York: I know it is almost heresy to say so, but I do not believe so strongly in the quantitative consideration of food. Some proteins agree with cardiac nephritic patients and some do not; it is a matter of individuality. The best method is to cut out all animal proteins and then find out by experiment what proteins are tolerated by the patient, beginning with those that have the best reputation, as cheese, chicken, etc. I cannot understand how, in the light of that great discovery at Rockefeller Institute—that amino-acids are stored in the tissues—such a belief could exist. Such investigations should be based on a consideration of the whole animal and the protein that is circulating in the blood. I would make a plea for a specific study of protein on individual patients. I believe that the quantitative work which leaves out the qualitative work on protein will not lead anywhere. I believe that no physician can benefit his patient more than by cutting out all protein, and by experiment, finding out what protein the patient can assimilate.

Dr. Leon Jonas, Philadelphia: We have been carrying on a similar line of work at the William Pepper Clinical Laboratory to determine the tolerance of various nephritics for protein. We first placed our patients on a low protein diet and then on a high protein diet, at the end of each period determining the amount of non-coagulable nitrogen in the blood according to the method of Folin. Our results agree with those of Dr. Frothingham. We also studied the blood-pressure and phthalein elimination, but not the salt content or urea elimination.

Dr. Walter L. Bierring, Des Moines, Ia.: It will be interesting to know to what extent Drs. Frothingham and Smillie have followed the classification as presented by Widal and Castaigne—sometimes referred to as the French conception of chronic nephritis. This regards the organ simply as a filter, the chief function of the kidney being: (1) to prevent the escape of albumin; (2) to eliminate the excess chlorid of sodium; (3) to eliminate the poisons which are ingested from without, or manufactured within. Castaigne classifies chronic nephritis in four groups: (1) chronic albuminuric nephritis; (2) hydropigenous nephritis (chloremic nephritis of Widal); (3) hydro-uric nephritis (uremic nephritis of Widal); (4) chronic hypertension, or cardiovascular nephritis. The practical conclusion to be drawn from the clasification applies especially to treatment. In the first group, a milk diet is not required, and a normal amount of salt, or a normal nitrogeneous diet is not injurious. The second group presents chronic parenchymatous nephritis, in which a salt-free diet is of prime importance. In the third type is recognized the familiar chronic interstitial nephritis in which, especially, a hyponitrogenous diet—starches, sugars, vegetables, fruit,

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and at times liberal quantities of water—is all-important. One is reluctant to accept the so-called cardiovascular nephritis as a definite type of chronic kidney disease. The study presented by Drs. Frothingham and Smillie suggests a marked change in our ideas of the proper diet in the different forms of chronic nephritis.

Dr. C. Frothingham, Jr., Boston: In answer to Dr. Rowntree's question I will say that the elimination of phenolsulphonephthalein varied slightly with the diets in the cases he mentioned. As the nitrogen in the blood rose the phthalein elimination fell slightly, and rose again as the blood nitrogen fell. The relation of the phthalein to the changes in diet was not marked or even present in many cases. No special type of protein was given. The patients were offered a general diet of ordinary foodstuffs. We would gladly eliminate all protein except the one the patients can best use, if there was any way of telling what can be best used. Work of this sort is an attempt to study the relation of patients and protein food. The urinary output was studied from day to day and is recorded on the charts. As it did not show anything of importance no mention was made of it. The classification of nephritis in this work has been based on the kidney's functional ability to excrete certain substances.

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